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☐	L8	songyang-zhou$.in.	5
☐	L7	lai-hung-sen$.in.	6
☐	L6	lai-hung$.in.	33
☐	L5	Nishikawa-kiyotaka$.in.	7
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☐	L4	WO-9811251-A1.did.	1
☐	L3	WO-9811251-A1.did.	1
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☐	L2	((library or libraries) near5 (peptide or polypeptide)) same tyrosine same kinase	93
☐	L1	((library or libraries) near5 (peptide or polypeptide or protein)) same tyrosine same kinase	202

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NEWS	4	FEB 28	BABS - Current-awareness alerts (SDIs) available
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NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
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NEWS	9	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	10	MAR 22	PATDPASPC - New patent database available
NEWS	11	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	12	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	13	APR 04	EMBASE - Database reloaded and enhanced
NEWS	14	APR 18	New CAS Information Use Policies available online
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NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS	17	MAY 23	GBFULL enhanced with patent drawing images
NEWS	18	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	19	JUN 06	STN Patent Forums to be held in June 2005
NEWS	20	JUN 06	The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS	21	JUN 13	RUSSIAPAT: New full-text patent database on STN
NEWS	22	JUN 13	FRFULL enhanced with patent drawing images
NEWS	23	JUN 20	MEDICONF to be removed from STN
NEWS	24	JUN 27	MARPAT displays enhanced with expanded G-group definitions and text labels
NEWS	25	JUL 01	MEDICONF removed from STN
NEWS	26	JUL 07	STN Patent Forums to be held in July 2005

NEWS EXPRESS	JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005
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FILE 'HOME' ENTERED AT 17:51:21 ON 08 JUL 2005

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=> (library or libraries) (5A) (peptide or polypeptide)
L1 14659 (LIBRARY OR LIBRARIES) (5A) (PEPTIDE OR POLYPEPTIDE)

=> tyrosine and kinase and l1
L2 394 TYROSINE AND KINASE AND L1

=> d scan l2

L2 394 ANSWERS CAPLUS COPYRIGHT 2005 ACS on STN
CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3, 6, 13
TI Differential expression of multiple isoforms of the ELKS mRNAs involved in a papillary thyroid carcinoma
ST papillary thyroid carcinoma ELKS isoform mRNA expression RET fusion; sequence protein ELKS splicing isoform cDNA human thyroid carcinoma
IT Chimeric gene, animal
Fusion proteins (chimeric proteins)
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ELKS-RET; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ELKS; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)
IT Proteins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study,

unclassified); PRP (Properties); BIOL (Biological study)
(ELKSα; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT Proteins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ELKSβ; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT Proteins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ELKSγ and fusion protein with RET; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT Proteins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ELKSδ and fusion protein with RET; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT Proteins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ELKSε and fusion protein with RET; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT Phosphorylation, biological
(autophosphorylation; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma in relation to)

IT Intestine
(colon; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT Brain
Human
Leukocyte
Ovary
Prostate gland
Protein sequences
Spleen
Testis
Thymus gland
Thyroid gland
Transcription, genetic
(differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT mRNA
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT Protein motifs
(differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma in relation to)

IT Genetic element
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(exon, optional; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

IT RNA splicing
(messenger, alternative; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid

carcinoma)
IT Thyroid gland, neoplasm
(papillary carcinoma; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)
IT Coiled-coil
(protein; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma in relation to)
IT Neurotrophic factor receptors
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ret, fusion proteins with ELKS isoforms; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ret, fusion with ELKS; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)
IT Pre-mRNA
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(splicing, alternative; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)
IT Carcinoma
(thyroid papillary; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)
IT 501180-79-6 501180-80-9 501180-81-0 501180-82-1 501180-83-2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)
IT 60-18-4, L-**Tyrosine**, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(autophosphorylation; differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma in relation to)
IT 146279-92-7D, Gene ret receptor protein **tyrosine kinase**, fusion proteins with ELKS isoforms
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(differential expression of multiple isoforms of ELKS mRNAs involved in fusion with RET in papillary thyroid carcinoma)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L2 394 ANSWERS BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Differential expression of multiple isoforms of the ELKS mRNAs involved in a papillary thyroid carcinoma.
IT Methods & Equipment
immunoprecipitation: detection method, immunological method, precipitation
IT Miscellaneous Descriptors
alternative splicing; gene structure: analysis

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):end

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L1 14659 (LIBRARY OR LIBRARIES) (5A) (PEPTIDE OR POLYPEPTIDE)
L2 394 TYROSINE AND KINASE AND L1

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1 FILES SEARCHED...
L3 209 PY>2000 AND L2

=> l2 not l3
L4 185 L2 NOT L3

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 95 DUP REM L4 (90 DUPLICATES REMOVED)

=> t ti l5 1-50

L5 ANSWER 1 OF 95 MEDLINE on STN
TI Using a phage display library to identify basic residues in A-Raf required to mediate binding to the Src homology 2 domains of the p85 subunit of phosphatidylinositol 3'-**kinase**.

L5 ANSWER 2 OF 95 MEDLINE on STN
TI **Peptide** and protein **library** screening defines optimal substrate motifs for AKT/PKB.

L5 ANSWER 3 OF 95 MEDLINE on STN DUPLICATE 1
TI Insights into the HER-2 receptor **tyrosine kinase** mechanism and substrate specificity using a transient kinetic analysis.

L5 ANSWER 4 OF 95 MEDLINE on STN
TI Combinatorial target-guided ligand assembly: identification of potent subtype-selective c-Src inhibitors.

L5 ANSWER 5 OF 95 MEDLINE on STN
TI Designing small-molecule switches for protein-protein interactions.

L5 ANSWER 6 OF 95 MEDLINE on STN
TI Identification of a peptide blocking vascular endothelial growth factor (VEGF)-mediated angiogenesis.

L5 ANSWER 7 OF 95 MEDLINE on STN
TI The molecular basis of FHA domain:phosphopeptide binding specificity and implications for phospho-dependent signaling mechanisms.

L5 ANSWER 8 OF 95 MEDLINE on STN DUPLICATE 2
TI A **peptide library** approach identifies a specific inhibitor for the ZAP-70 protein **tyrosine kinase**.

L5 ANSWER 9 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Highly efficient selection of phage antibodies mediated by display of antigen as Lpp-OmpA' fusions on live bacteria

L5 ANSWER 10 OF 95 MEDLINE on STN DUPLICATE 3
TI The specificity of the protein **kinase** C alpha, betaII and gamma isoforms as assessed by an unnatural alcohol-appended **peptide library**.

L5 ANSWER 11 OF 95 MEDLINE on STN
TI 14-3-3 proteins are required for the inhibition of Ras by exoenzyme S.

L5 ANSWER 12 OF 95 MEDLINE on STN
TI Protein engineering by expressed protein ligation.

L5 ANSWER 13 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Identification of the peptides that bind to **tyrosine kinase** receptor EphB2 by phage display

L5 ANSWER 14 OF 95 MEDLINE on STN
TI A designed peptidomimetic agonistic ligand of TrkA nerve growth factor receptors.

L5 ANSWER 15 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Screening of bioactive peptides that bind to **tyrosine kinase** receptor EphB2

L5 ANSWER 16 OF 95 MEDLINE on STN
TI Evolutionary history of the uterine serpins.

L5 ANSWER 17 OF 95 MEDLINE on STN DUPLICATE 4
TI Investigating the substrate specificity of the HER2/Neu **tyrosine kinase** using **peptide libraries**.

L5 ANSWER 18 OF 95 MEDLINE on STN
TI Characterisation and specificity of two single-chain Fv antibodies directed to the protein **tyrosine kinase** Syk.

L5 ANSWER 19 OF 95 MEDLINE on STN
TI Identification of natural ligands for SH2 domains from a phage display cDNA library.

L5 ANSWER 20 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Multiple target screening of molecular libraries by mass spectrometry

L5 ANSWER 21 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Substrates and pseudosubstrates for protein **kinase** lck and their use in inhibiting protein **kinase** lck

L5 ANSWER 22 OF 95 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI Isolated **tyrosine kinase** associated protein useful in the diagnosis and treatment of TKA-1 associated diseases.

L5 ANSWER 23 OF 95 MEDLINE on STN
TI Vascular endothelial growth factor (VEGF) receptor II-derived peptides inhibit VEGF.

L5 ANSWER 24 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 5
TI A novel peptide-SH3 interaction.

L5 ANSWER 25 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI The carboxyl terminus of B class ephrins constitutes a PDZ domain binding motif.

L5 ANSWER 26 OF 95 MEDLINE on STN
TI SH3 domains with high affinity and engineered ligand specificities targeted to HIV-1 Nef.

L5 ANSWER 27 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Combinatorial **peptide libraries** and molecular recognition in T-cell mediated immune response

L5 ANSWER 28 OF 95 MEDLINE on STN
TI Genetic selection of peptide inhibitors of biological pathways.

L5 ANSWER 29 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 6
TI Identification of residues involved in v-Src substrate recognition by site-directed mutagenesis.

L5 ANSWER 30 OF 95 MEDLINE on STN
TI Benzodiazepine compounds as inhibitors of the src protein **tyrosine kinase**: screening of a combinatorial library of 1,4-benzodiazepines.

L5 ANSWER 31 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 7
TI p561ck SH2 domain binding motifs from bead binding screening of **peptide libraries** containing phosphotyrosine surrogates.

L5 ANSWER 32 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI New antitumor leads from a peptidomimetic library.

L5 ANSWER 33 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI ATM and lymphoid malignancies; use of oriented **peptide libraries** to identify novel substrates of ATM critical in downstream signaling pathways

L5 ANSWER 34 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Design and synthesis of novel src homology-2 domain inhibitors

L5 ANSWER 35 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Synthesis and application of **tyrosine kinase** substrate libraries

L5 ANSWER 36 OF 95 MEDLINE on STN DUPLICATE 8
TI Phage display in proteolysis and signal transduction.

L5 ANSWER 37 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 9
TI Detection of substrate recognition by protein kinases and phosphatases

L5 ANSWER 38 OF 95 MEDLINE on STN
TI Studying receptor-ligand interactions using encoded amino acid scanning.

L5 ANSWER 39 OF 95 MEDLINE on STN
TI Peptides derived from self-proteins as partial agonists and antagonists of human CD8+ T-cell clones reactive to melanoma/melanocyte epitope MART1(27-35).

L5 ANSWER 40 OF 95 MEDLINE on STN DUPLICATE 10
TI Comparison of the intrinsic **kinase** activity and substrate specificity of c-Abl and Bcr-Abl.

L5 ANSWER 41 OF 95 MEDLINE on STN DUPLICATE 11
TI Application of "one-bead one-compound" combinatorial library methods in signal transduction research.

L5 ANSWER 42 OF 95 MEDLINE on STN DUPLICATE 12
TI Signal transduction by the peptide which mimics the activity of thrombopoietin.

L5 ANSWER 43 OF 95 MEDLINE on STN
TI Solid phase synthesis of a biased mini tetrapeptoid-library for the

discovery of monodentate ITAM mimics as ZAP-70 inhibitors.

L5 ANSWER 44 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Characterization of antigen-antibody interactions using single substitution analogs and mixture-based synthetic combinatorial libraries

L5 ANSWER 45 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Src Homology-2 Domains: Structure, mechanisms, and drug discovery.

L5 ANSWER 46 OF 95 MEDLINE on STN DUPLICATE 13
TI Protein **tyrosine** kinases: structure, substrate specificity, and drug discovery.

L5 ANSWER 47 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI 'Signal transduction targets: Structure, mechanisms, and drug discovery'. Editorial.

L5 ANSWER 48 OF 95 MEDLINE on STN DUPLICATE 14
TI Peptide and protein phosphorylation by protein **tyrosine kinase** Csk: insights into specificity and mechanism.

L5 ANSWER 49 OF 95 MEDLINE on STN DUPLICATE 15
TI Use of **peptide libraries** to determine optimal substrates of **tyrosine** kinases.

L5 ANSWER 50 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Application of the one-bead one-compound combinatorial library method in protein **tyrosine kinase** and cell surface receptor research

=> t ti 51-95

L5 ANSWER 51 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Exploring the Specificity Pockets of Two Homologous SH3 Domains Using Structure-Based, Split-Pool Synthesis and Affinity-Based Selection

L5 ANSWER 52 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI L-Dopa: A Powerful Nonphosphorylatable **Tyrosine** Mimetic for pp60c-src

L5 ANSWER 53 OF 95 MEDLINE on STN DUPLICATE 16
TI Potent pseudosubstrate-based peptide inhibitors for p60(c-src) protein **tyrosine kinase**.

L5 ANSWER 54 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Identification of high potency microbial and self ligands for a human autoreactive class II-restricted T cell clone

L5 ANSWER 55 OF 95 MEDLINE on STN DUPLICATE 17
TI Modified phage **peptide libraries** as a tool to study specificity of phosphorylation and recognition of **tyrosine** containing peptides.

L5 ANSWER 56 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 18
TI Identification of phosphopeptide ligands for the Src-homology 2 (SH2) domain of Grb2 by phage display.

L5 ANSWER 57 OF 95 MEDLINE on STN DUPLICATE 19

TI Sequence specificity of C-terminal Src **kinase** (CSK)--a comparison with Src-related kinases c-Fgr and Lyn.

L5 ANSWER 58 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 20
TI A study of Src SH2 domain protein-phosphopeptide binding interactions by electrospray ionization mass spectrometry

L5 ANSWER 59 OF 95 MEDLINE on STN
TI Recognition of unique carboxyl-terminal motifs by distinct PDZ domains.

L5 ANSWER 60 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Preparation of peptides and compounds that bind to SH2 (src homology region 2) domains of proteins and methods for their identification

L5 ANSWER 61 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Identification of Itk/Tsk Src homology 3 domain ligands

L5 ANSWER 62 OF 95 MEDLINE on STN DUPLICATE 21
TI Rapid identification of phosphopeptide ligands for SH2 domains. Screening of **peptide libraries** by fluorescence-activated bead sorting.

L5 ANSWER 63 OF 95 MEDLINE on STN DUPLICATE 22
TI Specificity of LIM domain interactions with receptor **tyrosine** kinases.

L5 ANSWER 64 OF 95 MEDLINE on STN DUPLICATE 23
TI The multiple endocrine neoplasia type 2B point mutation alters long-term regulation and enhances the transforming capacity of the epidermal growth factor receptor.

L5 ANSWER 65 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Mapping the specificity of an antibody against an oncogenic sequence using **peptide** combinatorial **libraries** and substitution analogs: Implications for breast cancer detection

L5 ANSWER 66 OF 95 MEDLINE on STN DUPLICATE 24
TI Identification of GIYWHHY as a novel peptide substrate for human p60c-src protein **tyrosine kinase**.

L5 ANSWER 67 OF 95 MEDLINE on STN DUPLICATE 25
TI Catalytic specificity of phosphotyrosine kinases Blk, Lyn, c-Src and Syk as assessed by phage display.

L5 ANSWER 68 OF 95 MEDLINE on STN DUPLICATE 26
TI Substrate specificity and inhibitor profile of human recombinant p56lck from a baculovirus expression vector.

L5 ANSWER 69 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 27
TI Development of a selective pseudosubstrate-based peptide inhibitor of pp60-c-src protein **tyrosine kinase**.

L5 ANSWER 70 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 28
TI Structure-activity relationship of a novel peptide substrate for p60-c-src protein **tyrosine kinase**.

L5 ANSWER 71 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Protein Structure-Based Design of Combinatorial **Libraries**: Discovery of Non-**Peptide** Binding Elements to Src SH3 Domain

L5 ANSWER 72 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Identification and characterization of a novel peptide substrate for P60c-src protein **tyrosine kinase** using a one-bead one-**peptide** combinatorial **peptide library** method

L5 ANSWER 73 OF 95 MEDLINE on STN DUPLICATE 29
TI Tight-binding inhibitory sequences against pp60(c-src) identified using a random 15-amino-acid **peptide library**.

L5 ANSWER 74 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI **Tyrosine** protein **kinase** assays.

L5 ANSWER 75 OF 95 MEDLINE on STN DUPLICATE 30
TI Amino-terminal sequence determinants for substrate recognition by platelet-derived growth factor receptor **tyrosine kinase**

L5 ANSWER 76 OF 95 MEDLINE on STN
TI Exploring antibody polyspecificity using synthetic combinatorial libraries.

L5 ANSWER 77 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI The structural basis for specificity in protein-**tyrosine kinase** signaling

L5 ANSWER 78 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
TI Methods for determining the phosphorylation site and substrate specificity of protein kinases

L5 ANSWER 79 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI The specificity of the transforming growth factor β receptor kinases determined by a spatially addressable **peptide library**.

L5 ANSWER 80 OF 95 MEDLINE on STN DUPLICATE 31
TI Identification of efficient pentapeptide substrates for the **tyrosine kinase** pp60c-src.

L5 ANSWER 81 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 32
TI Proline-rich sequences that bind to Src homology 3 domains with individual specificities.

L5 ANSWER 82 OF 95 MEDLINE on STN DUPLICATE 33
TI Identification and characterization of a novel synthetic peptide substrate specific for Src-family protein **tyrosine** kinases.

L5 ANSWER 83 OF 95 MEDLINE on STN DUPLICATE 34
TI Catalytic specificity of protein-**tyrosine** kinases is critical for selective signalling.

L5 ANSWER 84 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Identification and characterization of a novel peptide substrate specific for Src-family protein **tyrosine kinase** using a combinatorial **peptide library** method.

L5 ANSWER 85 OF 95 MEDLINE on STN DUPLICATE 35
TI Recognition and specificity in protein **tyrosine kinase** -mediated signalling.

L5 ANSWER 86 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Use of phage **peptide libraries** for studying the specificity of **tyrosine** phosphorylation and recognition.

L5 ANSWER 87 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 36
TI Discovery, development, and testing of substrates and inhibitors of PP60-C-SRC.

L5 ANSWER 88 OF 95 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI Identifying anti-proliferative peptide(s) which specifically bind to immunoglobulin super-family species idiotype - especially to inhibit B-cell lymphoma and leukocytic leukaemia cell proliferation, for anti-idiotype therapy.

L5 ANSWER 89 OF 95 MEDLINE on STN DUPLICATE 37
TI Use of synthetic **peptide libraries** and phosphopeptide-selective mass spectrometry to probe protein **kinase** substrate specificity.

L5 ANSWER 90 OF 95 MEDLINE on STN
TI Identification of Src, Fyn, Lyn, PI3K and Abl SH3 domain ligands using phage display libraries.

L5 ANSWER 91 OF 95 MEDLINE on STN DUPLICATE 38
TI Two binding orientations for peptides to the Src SH3 domain: development of a general model for SH3-ligand interactions.

L5 ANSWER 92 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI The use of **peptide libraries** to determine protein signaling pathways.

L5 ANSWER 93 OF 95 MEDLINE on STN
TI Cell adhesion and tumor metastasis.

L5 ANSWER 94 OF 95 MEDLINE on STN DUPLICATE 39
TI Molecular structure of a protein-**tyrosine**/threonine **kinase** activating p42 mitogen-activated protein (MAP) **kinase**: MAP **kinase kinase**.

L5 ANSWER 95 OF 95 MEDLINE on STN
TI Direct cloning of leucine zipper proteins: Jun binds cooperatively to the CRE with CRE-BP1.

=> d ibib abs 15

L5 ANSWER 1 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2001074400 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10967104
TITLE: Using a phage display library to identify basic residues in A-Raf required to mediate binding to the Src homology 2 domains of the p85 subunit of phosphatidylinositol 3'-**kinase**.
AUTHOR: King T R; Fang Y; Mahon E S; Anderson D H
CORPORATE SOURCE: Department of Biochemistry, University of Saskatchewan, Saskatoon, Saskatchewan S7N 5E5, Canada.
SOURCE: Journal of biological chemistry, (2000 Nov 17) 275 (46) 36450-6.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001229

AB Src homology 2 (SH2) domains are found in a variety of cytoplasmic proteins involved in mediating signals from cell surface receptors to various intracellular pathways. They fold as modular units and are capable of recognizing and binding to short linear peptide sequences containing a phosphorylated **tyrosine** residue. Here we show that each of the SH2 domains of the p85 subunit of phosphatidylinositol 3-**kinase** selects phage displayed peptide sequences containing the core (L/I)-A-(R/K)-I-R. The serine/threonine **kinase** A-Raf, containing the sequence LQRIRS, is associated with the p85 protein in both quiescent and growth factor stimulated cells. This suggests that p85 and A-Raf exist in a protein complex in cells and that complex formation does not require growth factor stimulation. We also show that p85 and A-Raf can bind directly to each other in vitro and that this interaction is mediated in part by the p85 SH2 domains. Further, the p85 SH2 domains require at least one of four distinct basic-X-basic sequence motifs within A-Raf for binding. This is the first description of a phosphotyrosine-independent SH2 domain interaction that requires basic residues on the SH2 ligand.

=> d ibib abs 15 2-95

L5 ANSWER 2 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2001074355 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10945990
TITLE: **Peptide** and protein **library** screening defines optimal substrate motifs for AKT/PKB.
AUTHOR: Obata T; Yaffe M B; Leparc G G; Piro E T; Maegawa H; Kashiwagi A; Kikkawa R; Cantley L C
CORPORATE SOURCE: Departments of Medicine and Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215, USA.
CONTRACT NUMBER: GM56203 (NIGMS)
SOURCE: Journal of biological chemistry, (2000 Nov 17) 275 (46) 36108-15.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001229

AB AKT was originally identified as a proto-oncogene with a pleckstrin homology and Ser/Thr protein **kinase** domains. Recent studies revealed that AKT regulates a variety of cellular functions including cell survival, cell growth, cell differentiation, cell cycle progression, transcription, translation, and cellular metabolism. To clarify the substrate specificity of AKT, we have used an oriented **peptide** **library** approach to determine optimal amino acids at positions N-terminal and C-terminal to the site of phosphorylation. The predicted optimal peptide substrate (Arg-Lys-Arg-Xaa-Arg-Thr-Tyr-Ser*-Phe-Gly where Ser* is the phosphorylation site) has similarities to but is distinct from optimal substrates that we previously defined for related basophilic

protein kinases such as protein **kinase** A, Ser/Arg-rich kinases, and protein **kinase** C family members. The positions most important for high V(max)/K(m) ratio were Arg-3>Arg-5>Arg-7. The substrate specificity of AKT was further investigated by screening a lambdaGEX phage HeLa cell cDNA expression library. All of the substrates identified by this procedure contained Arg-Xaa-Arg-Xaa-Xaa-(Ser/Thr) motifs and were in close agreement with the motif identified by **peptide library** screening. The results of this study should help in prediction of likely AKT substrates from primary sequences.

L5 ANSWER 3 OF 95 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2000417580 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10933796
TITLE: Insights into the HER-2 receptor **tyrosine kinase** mechanism and substrate specificity using a transient kinetic analysis.
AUTHOR: Jan A Y; Johnson E F; Diamonti A J; Carraway III K L; Anderson K S
CORPORATE SOURCE: Department of Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06520-8066, USA.
CONTRACT NUMBER: CA71702 (NCI)
GM07205 (NIGMS)
SOURCE: Biochemistry, (2000 Aug 15) 39 (32) 9786-803.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000905

AB The HER-2/erbB-2/c-neu proto-oncogene encodes for an EGF receptor-like protein which has been implicated in the pathogenesis of several human malignancies. Although much has been learned about the physiological significance of this receptor **tyrosine kinase**, its catalytic mechanism remains poorly understood. We have expressed, purified, and characterized two recombinant proteins corresponding to a full-length (HCD) and truncated (HKD) construct of the HER-2 intracellular **tyrosine kinase** domain and have identified an optimal substrate (GGMEDIYFEFMGGKKK; HER2Peptide) through screening of a degenerate **peptide library**. We have conducted a transient kinetic analysis of the HER-2 proteins (HCD and HKD) to illuminate mechanistic details of the HER-2 pathway. In particular, stopped-flow fluorescence studies with mant (N-methylanthraniloyl)-nucleotide derivatives provided direct measurements of the association and dissociation rate constants for these nucleotide interactions with the HER-2 recombinant proteins, thereby enabling the determination of nucleotide K(d) values. Moreover, the actual step of chemical catalysis was isolated using rapid chemical quench techniques and shown to occur approximately 3-fold faster than the steady-state rate which corresponds to product release. Evidence is also provided that suggests a conformational change that is partially rate-limiting at least in HCD. Furthermore, the role that the phosphorylation state of the protein may play on catalysis was examined. Studies carried out with pre-phosphorylated recombinant HER-2 proteins suggest that while autophosphorylation is not a prerequisite for enzymatic activity, this protein modification actually directly affects the catalytic mechanism by enhancing the rate of ADP release and that of the rate-limiting step. While a pre-steady-state kinetic analysis has been carried out on the catalytic subunit of cAMP-dependent serine/threonine **kinase**, to

our knowledge, this study represents the first reported transient kinetic investigation of a receptor **tyrosine kinase**. This work serves as a basis for comparison of these two important protein **kinase** families and in this report we highlight these similarities and differences.

L5 ANSWER 4 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2000183903 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10716979
TITLE: Combinatorial target-guided ligand assembly: identification of potent subtype-selective c-Src inhibitors.
AUTHOR: Maly D J; Choong I C; Ellman J A
CORPORATE SOURCE: Department of Chemistry, University of California, Berkeley, CA 94720, USA.
CONTRACT NUMBER: GM50353 (NIGMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2000 Mar 14) 97 (6) 2419-24. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000425

AB A method for the rapid and efficient identification of ligands to biological targets is reported. The combinatorial method does not require structural or mechanistic information and is accomplished in four straightforward steps. (i) A set of potential binding elements is prepared wherein each molecule incorporates a common chemical linkage group. (ii) The set of potential binding elements is screened to identify all binding elements that interact even weakly with the biological target. (iii) A combinatorial library of linked binding elements is prepared whereby the binding elements are connected by the common chemical linkage groups through a set of flexible linkers. (iv) The combinatorial library is screened to identify the tightest-binding ligands. The utility of the method was demonstrated by the identification of a potent and subtype-selective small molecule inhibitor of the non-receptor **tyrosine kinase** c-Src (IC(50) = 64 nM). Because the method relies on connecting two distinct binding elements, the relative contributions of the two binding elements to the potency and selectivity of the inhibitor were readily determined. This information provides valuable insight into the molecular basis of inhibition.

L5 ANSWER 5 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2000316207 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10856217
TITLE: Designing small-molecule switches for protein-protein interactions.
AUTHOR: Guo Z; Zhou D; Schultz P G
CORPORATE SOURCE: Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.
SOURCE: Science, (2000 Jun 16) 288 (5473) 2042-5. Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000706

Last Updated on STN: 20000706
Entered Medline: 20000628

AB Mutations introduced into human growth hormone (hGH) (Thr175 --> Gly-hGH) and the extracellular domain of the hGH receptor (Trp104 --> Gly-hGHbp) created a cavity at the protein-protein interface that resulted in binding affinity being reduced by a factor of 10(6). A small library of indole analogs was screened for small molecules that bind the cavity created by the mutations and restore binding affinity. The ligand 5-chloro-2-trichloromethylimidazole was found to increase the affinity of the mutant hormone for its receptor more than 1000-fold. Cell proliferation and JAK2 phosphorylation assays showed that the mutant hGH activates growth hormone signaling in the presence of added ligand. This approach may allow other protein-protein and protein-nucleic acid interactions to be switched on or off by the addition or depletion of exogenous small molecules.

L5 ANSWER 6 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2000211395 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10747021
TITLE: Identification of a peptide blocking vascular endothelial growth factor (VEGF)-mediated angiogenesis.
AUTHOR: Binetruy-Tournaire R; Demangel C; Malavaud B; Vassy R; Rouyre S; Kraemer M; Plouet J; Derbin C; Perret G; Mazie J C
CORPORATE SOURCE: Universite Paris XIII, UFR Leonard de Vinci, UPRES 2360, 'Ciblage Fonctionnel des Tumeurs Solides', 74 rue Marcel Cachin, 93017 Bobigny Cedex, France.. tournair@unice.fr
SOURCE: EMBO journal, (2000 Apr 3) 19 (7) 1525-33.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000515

AB Vascular endothelial growth factor (VEGF) binding to the **kinase** domain receptor (KDR/FLK1 or VEGFR-2) mediates vascularization and tumor-induced angiogenesis. Since there is evidence that KDR plays an important role in tumor angiogenesis, we sought to identify peptides able to block the VEGF-KDR interaction. A phage epitope library was screened by affinity for membrane-expressed KDR or for an anti-VEGF neutralizing monoclonal antibody. Both strategies led to the isolation of peptides binding KDR specifically, but those isolated by KDR binding tended to display lower reactivities. Of the synthetic peptides corresponding to selected clones tested to determine their inhibitory activity, ATWLPPR completely abolished VEGF binding to cell-displayed KDR. In vitro, this effect led to the inhibition of the VEGF-mediated proliferation of human vascular endothelial cells, in a dose-dependent and endothelial cell type-specific manner. Moreover, in vivo, ATWLPPR totally abolished VEGF-induced angiogenesis in a rabbit corneal model. Taken together, these data demonstrate that ATWLPPR is an effective antagonist of VEGF binding, and suggest that this peptide may be a potent inhibitor of tumor angiogenesis and metastasis.

L5 ANSWER 7 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2002052522 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11106755
TITLE: The molecular basis of FHA domain:phosphopeptide binding specificity and implications for phospho-dependent signaling mechanisms.

AUTHOR: Durocher D; Taylor I A; Sarbassova D; Haire L F; Westcott S L; Jackson S P; Smerdon S J; Yaffe M B
CORPORATE SOURCE: Wellcome Trust/Cancer Research Campaign Institute of Cancer and Developmental Biology and Department of Zoology University of Cambridge CB2 1QR, Cambridge, United Kingdom.
CONTRACT NUMBER: GM60594 (NIGMS)
HL03601 (NHLBI)
SOURCE: Molecular cell, (2000 Nov) 6 (5) 1169-82.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1G6G
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020125
Entered Medline: 20020122

AB Forkhead-associated (FHA) domains are a class of ubiquitous signaling modules that appear to function through interactions with phosphorylated target molecules. We have used oriented **peptide library** screening to determine the optimal phosphopeptide binding motifs recognized by several FHA domains, including those within a number of DNA damage checkpoint kinases, and determined the X-ray structure of Rad53p-FHA1, in complex with a phospho-threonine peptide, at 1.6 A resolution. The structure reveals a striking similarity to the MH2 domains of Smad tumor suppressor proteins and reveals a mode of peptide binding that differs from SH2, 14-3-3, or PTB domain complexes. These results have important implications for DNA damage signaling and CHK2-dependent tumor suppression, and they indicate that FHA domains play important and unsuspected roles in S/T **kinase** signaling mechanisms in prokaryotes and eukaryotes.

L5 ANSWER 8 OF 95 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001040371 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11090635
TITLE: A **peptide library** approach identifies a specific inhibitor for the ZAP-70 protein **tyrosine kinase**.
AUTHOR: Nishikawa K; Sawasdikosol S; Fruman D A; Lai J; Songyang Z; Burakoff S J; Yaffe M B; Cantley L C
CORPORATE SOURCE: Division of Signal Transduction, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: AI7258 (NIAID)
GM56203 (NIGMS)
SOURCE: Molecular cell, (2000 Oct) 6 (4) 969-74.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010625
Entered Medline: 20001207

AB We utilized a novel **peptide library** approach to identify specific inhibitors of ZAP-70, a protein Tyr **kinase** involved in T cell activation. By screening more than 6 billion peptides oriented by a common Tyr residue for their ability to bind to ZAP-70, we determined a consensus optimal peptide. A Phe-for-Tyr substituted version of the peptide inhibited ZAP-70 protein Tyr **kinase** activity by competing with protein substrates (K(I) of 2 microM). The related protein

Tyr kinases, Lck and Syk, were not significantly inhibited by the peptide. When introduced into intact T cells, the peptide blocked signaling downstream of ZAP-70, including ZAP-70-dependent gene induction, without affecting upstream Tyr phosphorylation. Thus, screening Tyr-oriented **peptide libraries** can identify selective **peptide** inhibitors of protein Tyr kinases.

L5 ANSWER 9 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:606604 CAPLUS
DOCUMENT NUMBER: 133:308767
TITLE: Highly efficient selection of phage antibodies mediated by display of antigen as Lpp-OmpA' fusions on live bacteria
AUTHOR(S): Benhar, Itai; Azriel, Ronit; Nahary, Limor; Shaky, Shelly; Berdichevsky, Yevgeny; Tamarkin, Aviva; Wels, Winfried
CORPORATE SOURCE: Department of Molecular Microbiology and Biotechnology, George S. Wise Faculty of Life Sciences, Tel-Aviv University, Ramat Aviv, Israel
SOURCE: Journal of Molecular Biology (2000), 301(4), 893-904
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Delayed infectivity panning (DIP) is a novel approach for the in vivo isolation of interacting protein pairs. DIP combines phage display and cell surface display of polypeptides as follows: an antigen is displayed in many copies on the surface of F+ Escherichia coli cells by fusing it to a Lpp-OmpA' hybrid. To prevent premature, non-specific infection by phage, the cells are rendered functionally F- by growth at 16°. The antigen-displaying cells are used to capture antibody-displaying phage by virtue of the antibody-antigen interaction. Following removal of unbound phage, infection of the cells by bound phage is initiated by raising the temperature to 37° that facilitates F pilus expression. The phage then dissociate from the antigen and infect the bacteria through the F pilus. Using specific scFv antibodies and the human ErbB2 proto-oncogene and IL2-Rα chain as model antibody-antigen pairs, the authors demonstrate enrichment of those phage that display a specific antibody over phage that display an irrelevant antibody of over 1,000,000 in a single DIP cycle. The authors further show the successful isolation of anti-toxin, anti-receptor, anti-enzyme and anti-**peptide** antibodies from several immune phage **libraries**, a shuffled library and a large synthetic human library. The effectiveness of DIP makes it suitable for the isolation of rare clones present in large libraries. Since DIP can be applied for most of the phage libraries already existing, it could be a powerful tool for the rapid isolation and characterization of binders in numerous protein-protein interactions. (c) 2000 Academic Press.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 95 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001086717 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10903131
TITLE: The specificity of the protein **kinase** C alpha, betaII and gamma isoforms as assessed by an unnatural alcohol-appended **peptide library**.
AUTHOR: Yan X; Curley K; Lawrence D S
CORPORATE SOURCE: Department of Biochemistry, The Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Ave., Bronx, New York, NY 10461, USA.
CONTRACT NUMBER: GM45989 (NIGMS)

SOURCE: Biochemical journal, (2000 Aug 1) 349 Pt 3 709-15.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB Previous studies using conventional **peptide**-based **libraries** have demonstrated that homologous protein-processing enzymes [e.g. the alpha, betaII and gamma isoforms of protein **kinase** (PKC)] typically display identical amino acid consensus sequences. These observations have hampered the acquisition of selective synthetic substrates for the individual members of these enzyme families. We describe here a parallel synthesis strategy, readily adaptable to the preparation of large libraries, that has led to the emergence of the first examples of selective substrates for the conventional PKC isoforms. In addition, we have found that a wide variety of structurally diverse N-appended alcohol-containing residues, including **tyrosine**, serve as substrates for the PKC alpha, betaII and gamma isoforms. This broad active-site substrate specificity with respect to both natural and unnatural residues may prove to be especially applicable to the construction of transition-state analogues and suicide substrates, species that often require the presence of structurally elaborate functionality.

L5 ANSWER 11 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2001086715 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10903129
TITLE: 14-3-3 proteins are required for the inhibition of Ras by exoenzyme S.
AUTHOR: Henriksson M L; Troller U; Hallberg B
CORPORATE SOURCE: Cellular and Molecular Biology, University of Umea, S-901 87 Umea, Sweden.
SOURCE: Biochemical journal, (2000 Aug 1) 349 Pt 3 697-701.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20021218
Entered Medline: 20010118

AB 14-3-3 proteins play a regulatory role and participate in both signal transduction and checkpoint control pathways. 14-3-3 proteins bind phosphoserine ligands, such as Raf-1 **kinase** and Bad, by recognizing the phosphorylated consensus motif, Arg-Ser-Xaa-pSer-Xaa-Pro (where 'Xaa' represents 'any residue', and 'pSer' is 'phosphoserine'). However, 14-3-3 proteins must bind unphosphorylated ligands, such as glycoprotein Ibalpha and Pseudomonas aeruginosa exoenzyme S (ExoS), since it has been suggested that specific residues of 14-3-3 proteins are required for activation of ExoS. Furthermore, an unphosphorylated **peptide** derived from a phage display **library** inhibited the binding of both ExoS and Raf-1 to 14-3-3, and bound within the same conserved amphipathic groove on the surface of 14-3-3 as the Raf-derived phosphopeptide (pS-Raf-259). In the present study we identify the interaction site on ExoS for 14-3-3, and show that ExoS and 14-3-3 do indeed interact in vivo. In addition, we show that this interaction is critical for the ADP-ribosylation of Ras by ExoS, both in vitro and in vivo. Loss of the 14-3-3 binding site on ExoS results in an ExoS molecule

that is unable to efficiently inactivate Ras, and displays reduced killing activity.

L5 ANSWER 12 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2001127564 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11075362
TITLE: Protein engineering by expressed protein ligation.
AUTHOR: Blaschke U K; Silberstein J; Muir T W
CORPORATE SOURCE: Laboratory of Synthetic Protein Chemistry, Rockefeller University, New York, New York 10021, USA.
CONTRACT NUMBER: GM55843-01 (NIGMS)
SOURCE: Methods in enzymology, (2000) 328 478-96.
Journal code: 0212271. ISSN: 0076-6879.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222

AB By allowing the controlled assembly of synthetic peptides and recombinant polypeptides, expressed protein ligation permits unnatural amino acids, biochemical probes, and biophysical probes to be specifically incorporated into semisynthetic proteins. A powerful feature of the method is its modularity; once the reactive recombinant pieces are in hand and the optimal ligation conditions have been developed, it is possible to quickly generate an array of semisynthetic analogs by simply attaching different synthetic peptide cassettes--in most cases the synthetic peptides will be small and easy to make. From a practical perspective, the rate-determining step in the process is usually not the ligation step (it is based on a simple and efficient chemical reaction), but rather the generation of the reactive polypeptide building blocks. In particular, optimizing the yields of recombinant polypeptide building blocks can require some initial effort. However, it should be noted that the initial investment in time required to optimize the production of the recombinant fragment is offset by the ease and speed with which one can produce the material thereafter. In the example described in this chapter, the yield of soluble intein fusion protein was slightly better using the GyrA intein than for the VMA intein, although in both cases significant amounts of fusion protein were present in the cell pellet. Studies are currently underway to identify optimal refolding conditions for GyrA fusion proteins solubilized from inclusion bodies.

L5 ANSWER 13 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:736576 CAPLUS
DOCUMENT NUMBER: 135:15589
TITLE: Identification of the peptides that bind to **tyrosine kinase** receptor EphB2 by phage display
AUTHOR(S): Zhang, Xiao-Guang; Yao, Li-Bo; Han, Jiong; Liu, Xin-Ping; Han, Jing-Tian; Nie, Xiao-Yan; Su, Cheng-Zhi
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, The Fourth Military Medical University, Xi'an, 710032, Peop. Rep. China
SOURCE: Shengwu Huaxue Yu Shengwu Wuli Xuebao (2000), 32(5), 475-479
CODEN: SHWPAU; ISSN: 0582-9879
PUBLISHER: Shanghai Kexue Jishu Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The gene encoding the Ig-like domain of **tyrosine** protein

kinase receptor EphB2 was cloned into the expressing vector pET28a. Under induction with IPTG, the pos. strain expressed the fusion protein with a hexahistidine tail on the N-terminal. The protein was purified under denaturing conditions using metal chelate chromatog. The purity was up to 94%. The purified-protein-coated ELISA plate was used as target to screen recombinant phages able to bind onto it; and after three rounds of affinity screening, 19 phages that could bind specifically with EphB2 were isolated from a random phage-displayed seven-**peptide library**. The peptide sequences of the pos. phage clones were analyzed.

L5 ANSWER 14 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2000124066 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10648649
TITLE: A designed peptidomimetic agonistic ligand of TrkA nerve growth factor receptors.
AUTHOR: Maliartchouk S; Feng Y; Ivanisevic L; Debeir T; Cuello A C; Burgess K; Saragovi H U
CORPORATE SOURCE: Department of Pharmacology, McGill University, Montreal, Quebec, Canada H3G 1Y6.
CONTRACT NUMBER: CA 82642 (NCI)
GM 50772 (NIGMS)
SOURCE: Molecular pharmacology, (2000 Feb) 57 (2) 385-91.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000302

AB A proteolytically stable small molecule beta-turn peptidomimetic, termed D3, was identified as an agonist of the TrkA neurotrophin receptor. D3 binds the Ig-like C2 region of the extracellular domain of TrkA, competes the binding of another TrkA agonist, affords selective trophic protection to TrkA-expressing cell lines and neuronal primary cultures, and induces the differentiation of primary neuronal cultures. These results indicate that a small beta-turn peptidomimetic can activate a **tyrosine kinase** neurotrophin receptor that normally binds a relatively large protein ligand. Agents such as D3 that bind the extracellular domain of Trk receptors will be useful pharmacological agents to address disorders where Trk receptors play a role, by targeting populations selectively.

L5 ANSWER 15 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:803137 CAPLUS
DOCUMENT NUMBER: 135:148169
TITLE: Screening of bioactive peptides that bind to **tyrosine kinase** receptor EphB2
AUTHOR(S): Zhang, Xiaoguang; Han, Jiong; Han, Jingtian; Liu, Xinping; Yao, Libo; Nie, Xiaoyan; Su, Chengzhi
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Fourth Military Medical University, Xi'an, 710032, Peop. Rep. China
SOURCE: Mianyixue Zazhi (2000), 16(5), 342-345
CODEN: MIZAED; ISSN: 1000-8861
PUBLISHER: Mianyixue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The bioactive peptides binding to **tyrosine kinase** receptor EphB2 were screened and identified. The gene encoding the ligand

binding domain of EphB2 was cloned into the expressing vector pRSETA under induction with IPTG, and the fusion protein was expressed and purified under denaturing conditions by metal chelate chromatog. The purified protein coated on ELISA plate was used as target for three rounds of affinity selection. SDS-PAGE anal. showed that the fusion protein mainly existed in inclusion bodies. The purity was up to 95%. Thirteen pos. phages were isolated from a random phage- displayed twelve-**peptide library**. The results showed that peptides interacting specifically with EphB2 were obtained and there were common motifs among their sequences.

L5 ANSWER 16 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2000421335 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10931499
TITLE: Evolutionary history of the uterine serpins.
AUTHOR: Peltier M R; Raley L C; Liberles D A; Benner S A; Hansen P J
CORPORATE SOURCE: Department of Dairy and Poultry Sciences, University of Florida, Gainesville, Florida 32611-0920, USA.
CONTRACT NUMBER: GM 54075 (NIGMS)
HG 01729 (NHGRI)
SOURCE: Journal of experimental zoology, (2000 Aug 15) 288 (2) 165-74.
Journal code: 0375365. ISSN: 0022-104X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20020121
Entered Medline: 20000905

AB A bioinformatics analysis was conducted on the four members of the uterine serpin (US) family of serpins. Evolutionary analysis of the protein sequences and 86 homologous serpins by maximum parsimony and distance methods indicated that the uterine serpins proteins form a clade distinct from other serpins. Ancestral sequences were reconstructed throughout the evolutionary tree by parsimony. These suggested that some branches suffered a high ratio of nonsynonymous to synonymous mutations, suggesting episodes of adaptive evolution within the serpin family. Analysis of the sequences by neutral evolutionary distance methods suggested that the uterine serpins diverged from other serpins prior to the divergence of the mammals from other vertebrates. The porcine uterine serpins are paralogs that diverged from a single common ancestor within the Sus genus after pigs separated from other artiodactyls. The uterine serpins contain several protein **kinase** C and **tyrosine kinase** phosphorylation sites. These sites may be important for the lymphocyte-inhibitory activity of OvUS if, like other basic proteins, OvUS can cross the cell membrane of an activated lymphocyte. Internalized OvUS could serve as an alternative target to protein kinases important for the mitogenic response to antigens.

L5 ANSWER 17 OF 95 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001042535 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11053645
TITLE: Investigating the substrate specificity of the HER2/Neu **tyrosine kinase** using **peptide libraries**.
AUTHOR: Chan P M; Nestler H P; Miller W T
CORPORATE SOURCE: The Department of Physiology and Biophysics, Basic Science Tower, T-6, School of Medicine, State University of New York at Stony Brook, Stony Brook, NY 11794-8661, USA.

SOURCE: Cancer letters, (2000 Nov 28) 160 (2) 159-69.
Journal code: 7600053. ISSN: 0304-3835.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207

AB The product of the HER2/Neu oncogene is a receptor **tyrosine kinase** that is amplified in 25-30% of human primary breast tumors. In this project, we have isolated the HER2/Neu **kinase** from Sf9 cells infected with a baculovirus expression vector. We probed the substrate specificity of the HER2/Neu **kinase** using two **peptide libraries**: (1) a soluble **peptide library** containing three degenerate positions N-terminal to **tyrosine**; and (2) a bead-supported combinatorial library possessing six degenerate positions at P-1, P-2, P-3, P+1, P+2, and P+3. We identified four novel substrate sequences for HER2/Neu from the two **peptide libraries**. We synthesized these peptides as individual sequences and measured steady-state kinetic properties for phosphorylation by HER2/Neu. One of the peptides, AAEEIYAARRG, is the best synthetic peptide substrate reported to date for HER2/Neu. All of the sequences bear a resemblance to sites of autophosphorylation on HER2/Neu and related epidermal growth factor (EGF) receptor family **tyrosine** kinases.

L5 ANSWER 18 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2000164761 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10699584
TITLE: Characterisation and specificity of two single-chain Fv antibodies directed to the protein **tyrosine kinase** Syk.
AUTHOR: Peneff C; Lefranc M P; Dariavach P
CORPORATE SOURCE: Institut de Genetique Moleculaire de Montpellier, UMR CNRS 5535 (IFR 24), 1919 Route de Mende, 34293, Montpellier, France.
SOURCE: Journal of immunological methods, (2000 Mar 6) 236 (1-2) 105-15.
Journal code: 1305440. ISSN: 0022-1759.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000512
Last Updated on STN: 20001005
Entered Medline: 20000502

AB In order to obtain single chain Fv fragments (scFv) specific for the protein **tyrosine kinase** Syk, we screened a human synthetic phage-display library. Two glutathione S-transferase (GST):Syk fusion proteins containing both SH2 domains of Syk were used to perform three rounds of selection of the library. Among the scFv fragments resulting from the third round of selection, the ones specific for the GST portion of the fusion proteins were eliminated by performing enzyme-linked immunosorbent assay tests on GST:Syk versus GST coated plates, and the monoclonal scFv fragments binding only to the GST:Syk coated plates with high affinities were further analysed. We report here the in vitro characterisation of G4G11 and G6G2 anti-Syk scFvs. G4G11 shows the best performance in immunoprecipitation and immunofluorescence experiments, and G6G2 is able to detect Syk in immunoprecipitation, immunofluorescence and

on Western blots. Both scFvs are also able to detect the phosphorylated form of Syk, and neither of them binds to Zap-70, the other member of the Syk family of protein **tyrosine** kinases.

L5 ANSWER 19 OF 95 MEDLINE on STN
ACCESSION NUMBER: 2000171587 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10704309
TITLE: Identification of natural ligands for SH2 domains from a phage display cDNA library.
AUTHOR: Cochrane D; Webster C; Masih G; McCafferty J
CORPORATE SOURCE: Cambridge Antibody Technology, The Science Park, Melbourn, Cambridgeshire, SG8 6JJ, UK.
SOURCE: Journal of molecular biology, (2000 Mar 17) 297 (1) 89-97. Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000421
Last Updated on STN: 20000421
Entered Medline: 20000410

AB The cytoplasmic domain of the Fc gamma receptor IIB (FcgammaRIIB) can be successfully displayed on the surface of filamentous phage, and after phosphorylation in vitro, can interact specifically with the SH2 domains of SHP-2, a cytoplasmic **tyrosine** phosphatase. When full-length FcgammaRIIB is expressed on phage, however, this interaction is greatly compromised, illustrating that characteristics of the full-length sequence are not well tolerated by the phage display system. Many associations in cell physiology are driven by similar interactions involving small modular binding domains or ligands, and so a fragmented cDNA library will facilitate display of such domains free of sequences which compromise their expression. A fragmented leukocyte cDNA display library of 10(8) clones was constructed. This library was phosphorylated in vitro with fyn **kinase** and was selected against the tandem SH2 domains of SHP-2 in the search for additional ligands. A depletion strategy to remove non-specific clones was employed, using SHP-2 Sepharose, prior to in vitro phosphorylation and selection. This permitted the emergence of clones encoding the cytoplasmic domain of PECAM-1, another natural ligand for SHP-2. The importance of dual phosphorylation of **tyrosine** residues at positions 663 and 686 was confirmed in competition ELISA experiments using phosphorylated phage and synthetic peptides. Thus, phage display of fragmented cDNA libraries permits the identification and characterisation of phosphorylated ligands of modular binding domains based on their functional interaction.

L5 ANSWER 20 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:96389 CAPLUS
DOCUMENT NUMBER: 130:136293
TITLE: Multiple target screening of molecular libraries by mass spectrometry
INVENTOR(S): Hsieh, Yinliang F.
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9905309	A1	19990204	WO 1998-US15112	19980722
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9884147	A1	19990216	AU 1998-84147	19980722
PRIORITY APPLN. INFO.:			US 1997-53477P	P 19970723
			US 1998-22726	A 19980212
			WO 1998-US15112	W 19980722

AB The invention is based on the discovery that mass spectrometry can be used for screening a library of drug candidates for activity against multiple targets simultaneously. In general, the invention features a method of screening a mol. library of compds. for individual compds. that affect the ability of one or more of a plurality of target mols. (such as enzymes or other polypeptides or proteins) to catalyze the conversion of corresponding peptide substrates to products, or the reaction of a substrate with a target mol. to yield a product. The new methods allow both the drugs and the targets involved to be rapidly and accurately identified.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:808582 CAPLUS
DOCUMENT NUMBER: 132:46952
TITLE: Substrates and pseudosubstrates for protein **kinase** lck and their use in inhibiting protein **kinase** lck
INVENTOR(S): Cantley, Lewis C.; Songyang, Zhou
PATENT ASSIGNEE(S): Beth Israel Hospital, USA
SOURCE: U.S., 69 pp., Cont.-in-part of U.S. 5,532,167.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6004757	A	19991221	US 1995-369643	19950106
US 5532167	A	19960702	US 1994-178570	19940107
PRIORITY APPLN. INFO.:			US 1994-178570	A2 19940107
OTHER SOURCE(S):	MARPAT 132:46952			

AB The title peptides and their use are disclosed. A method for determining an amino acid sequence motif for a phosphorylation site of a protein **kinase** is disclosed and used to determine the lck substrate/pseudosubstrate peptides. In this method, a protein **kinase** is contacted with an oriented degenerate **peptide library**, peptides within the **library** which are substrates for the **kinase** are converted to phosphopeptides and the phosphopeptides are separated from non-phosphorylated peptides. The isolated phosphopeptides are sequenced and an amino acid sequence motif for the phosphorylation site is determined based upon the relative abundance of different amino acids residues at each degenerate position. Also disclosed are peptide substrates for protein **kinase** A, cell cycle control kinases (including cyclin B/p33cdc2 and cyclin A/p33CDK2), src family kinases (including pp60c-src and pp60v-src), EGF receptor, p92c-fpsfes, c-abl, and RET **tyrosine kinase** based upon amino acid sequence motifs for the phosphorylation sites of these kinases.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 95 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-508190 [42] WPIDS
CROSS REFERENCE: 1998-101049 [09]; 1999-417994 [35]
DOC. NO. CPI: C1999-148373
TITLE: Isolated **tyrosine kinase** associated protein useful in the diagnosis and treatment of TKA-1 associated diseases.
DERWENT CLASS: B04 D16
INVENTOR(S): SEEDORF, K; ULLRICH, A
PATENT ASSIGNEE(S): (PLAC) MAX PLANCK GES FOERDERUNG WISSENSCHAFTEN
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5945523	A	19990831	(199942)*		24

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5945523	A	Provisional	US 1995-5167P	19951013
		Provisional	US 1995-5423P	19951013
		CIP of	US 1996-665037	19960613
		CIP of	US 1996-666067	19960614
			US 1996-732870	19961015

PRIORITY APPLN. INFO: US 1996-732870 19961015; US 1995-5167P 19951013; US 1995-5423P 19951013; US 1996-665037 19960613; US 1996-666067 19960614
AN 1999-508190 [42] WPIDS
CR 1998-101049 [09]; 1999-417994 [35]
AB US 5945523 A UPAB: 19991014
NOVELTY - Isolated, enriched or purified **tyrosine kinase** associated protein (TKA-1) without a src homology region 2 (SH2) domain is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) an isolated, enriched or purified nucleic acid molecule comprising:

(a) a nucleotide sequence (I) encoding TKA-1 polypeptide which has the amino acid sequence of polypeptide (II) given in the specification but lacks one but not all of the following segments of amino acid residues; 7-89, 7-112, 146-229 or 146-252; or

(b) the complement of (I);

(2) a recombinant nucleic acid comprising (I);

(3) an expression vector comprising (I) operably linked to a regulatory nucleotide sequence that controls expression of the nucleic acid molecule in a host cell; and

(4) an isolated host cell transfected or transformed with nucleic acid molecule (I).

USE - In the diagnosis and treatment of TKA-1 associated diseases and conditions including cancer.

Dwg.0/2

L5 ANSWER 23 OF 95 MEDLINE on STN
ACCESSION NUMBER: 1999150346 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10026178
TITLE: Vascular endothelial growth factor (VEGF) receptor II-derived peptides inhibit VEGF.

AUTHOR: Piossek C; Schneider-Mergener J; Schirner M; Vakalopoulou E; Germeroth L; Thierauch K H
CORPORATE SOURCE: JERINI BIO TOOLS GMBH, Rudower Chaussee 5, 12489 Berlin, Germany.
SOURCE: Journal of biological chemistry, (1999 Feb 26) 274 (9) 5612-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 20000303
Entered Medline: 19990318

AB Vascular endothelial growth factor (VEGF) directly stimulates endothelial cell proliferation and migration via **tyrosine kinase** receptors of the split **kinase** domain family. It mediates vascular growth and angiogenesis in the embryo but also in the adult in a variety of physiological and pathological conditions. The potential binding site of VEGF with its receptor was identified using cellulose-bound overlapping peptides of the extracytosolic part of the human vascular endothelial growth factor receptor II (VEGFR II). Thus, a peptide originating from the third globular domain of the VEGFR II comprising residues 247RTELNVGIDFNWEYP261 was revealed as contiguous sequence stretch, which bound 125I-VEGF165. A systematic replacement with L-amino acids within the peptide representing the putative VEGF-binding site on VEGFR II indicates Asp255 as the hydrophilic key residue for binding. The dimerized peptide (RTELNVGIDFNWEYPAS)2K inhibits VEGF165 binding with an IC50 of 0.5 microM on extracellular VEGFR II fragments and 30 microM on human umbilical vein cells. VEGF165-stimulated autophosphorylation of VEGFR II as well as proliferation and migration of microvascular endothelial cells was inhibited by the monomeric peptide RTELNVGIDFNWEYPASK at a half-maximal concentration of 3-10, 0.1, and 0.1 microM, respectively. We conclude that transduction of the VEGF165 signal can be interrupted with a peptide derived from the third Ig-like domain of VEGFR II by blockade of VEGF165 binding to its receptor.

L5 ANSWER 24 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 5
ACCESSION NUMBER: 2000:8399 BIOSIS
DOCUMENT NUMBER: PREV200000008399
TITLE: A novel peptide-SH3 interaction.
AUTHOR(S): Mongiovi, Adriana Maria; Romano, Pascale R.; Panni, Simona; Mendoza, Manuel; Wong, William T.; Musacchio, Andrea; Cesareni, Gianni; Di Fiore, Pier Paolo [Reprint author]
CORPORATE SOURCE: Department of Experimental Oncology, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy
SOURCE: EMBO (European Molecular Biology Organization) Journal, (Oct. 1, 1999) Vol. 18, No. 19, pp. 5300-5309. print.
CODEN: EMJODG. ISSN: 0261-4189.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Dec 1999
Last Updated on STN: 31 Dec 2001

AB SH3 domains constitute a family of protein-protein interaction modules that bind to peptides displaying an X-proline-X-X-proline (XPXXP) consensus. We report that the SH3 domain of Eps8, a substrate of receptor and non-receptor **tyrosine** kinases, displays a novel and unique binding preference. By a combination of approaches including (i) screening of phage-displayed random **peptide libraries**, (ii) mapping of the binding regions on three physiological interactors of

Eps8, (iii) alanine scanning of binding peptides and (iv) in vitro cross-linking, we demonstrate that a proline-X-X-aspartate-**tyrosine** (PXXDY) consensus is indispensable for binding to the SH3 domain of Eps8. Screening of the Expressed Sequence Tags database allowed the identification of three Eps8-related genes, whose SH3s also display unusual binding preferences and constitute a phylogenetically distinct subfamily within the SH3 family. Thus, Eps8 identifies a novel family of SH3-containing proteins that do not bind to can onical XPXXP-containing peptides, and that establish distinct interactions in the signaling network.

L5 ANSWER 25 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999060351 EMBASE
TITLE: The carboxyl terminus of B class ephrins constitutes a PDZ domain binding motif.
AUTHOR: Lin D.; Gish G.D.; Songyang Z.; Pawson T.
CORPORATE SOURCE: T. Pawson, Programme in Molecular Biol./Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, 600 University Avenue, Toronto, Ont. M5G 1X5, Canada. pawson@mshri.on.ca
SOURCE: Journal of Biological Chemistry, (5 Feb 1999) Vol. 274, No. 6, pp. 3726-3733.
Refs: 55
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19990304
Last Updated on STN: 19990304

AB Ephrin B proteins function as ligands for B class Eph receptor **tyrosine** kinases and are postulated to possess an intrinsic signaling function. The sequence at the carboxyl terminus of B-type ephrins contains a putative PDZ binding site, providing a possible mechanism through which transmembrane ephrins might interact with cytoplasmic proteins. To test this notion, a day 10.5 mouse embryonic expression **library** was screened with a biotinylated **peptide** corresponding to the carboxyl terminus of ephrin B3. Three of the positive cDNAs encoded polypeptides with multiple PDZ domains, representing fragments of the molecule GRIP, the protein syntenin, and PHIP, a novel PDZ domain-containing protein related to Caenorhabditis elegans PAR-3. In addition, the binding specificities of PDZ domains previously predicted by an oriented library approach (Songyang, Z., Fanning, A. S., Fu, C., Xu, J., Marfatia, S. M., Chishti, A. H., Crompton, A., Chan, A. C., Anderson, J. M., and Cantley, L. C. (1997) Science 275, 73-77) identified the **tyrosine** phosphatase FAP-1 as a potential binding partner for B ephrins. In vitro studies demonstrated that the fifth PDZ domain of FAP-1 and full-length syntenin bound ephrin B1 via the carboxyl-terminal motif. Lastly, syntenin and ephrin B1 could be co-immunoprecipitated from transfected COS-1 cells, suggesting that PDZ domain binding of B ephrins can occur in cells. These results indicate that the carboxyl-terminal motif of B ephrins provides a binding site for specific PDZ domain-containing proteins, which might localize the transmembrane ligands for interactions with Eph receptors or participate in signaling within ephrin B-expressing cells.

L5 ANSWER 26 OF 95 MEDLINE on STN

ACCESSION NUMBER: 2000016380 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10547288
TITLE: SH3 domains with high affinity and engineered ligand

specificities targeted to HIV-1 Nef.
AUTHOR: Hiipakka M; Poikonen K; Saksela K
CORPORATE SOURCE: Institute of Medical Technology, University of Tampere, Tampere, FIN-33101, Finland.
SOURCE: Journal of molecular biology, (1999 Nov 12) 293 (5) 1097-106.
Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000111

AB The avid binding of HIV-1 Nef to the Src homology-3 (SH3) domain of Hck (KD 250 nM) has been shown to involve an interaction between the RT-loop of Hck-SH3 and residues in Nef outside of its prototypic polyproline type II (PPII) helix-containing SH3-ligand region. Such distinctive interactions are thought to provide specificity and affinity for other SH3/ligand protein complexes as well. Here, we have constructed and successfully displayed on the surface of M13 bacteriophage particles a complex library of SH3 domains, which are derived from Hck but carry a random hexapeptide substitution in their RT-loops (termed RRT-SH3). Using this strategy we have identified individual RRT-SH3 domains that can bind to Nef up to 40-fold more avidly than Hck-SH3. Some of these high-affinity RRT-SH3 domains resembled Hck-SH3 in that they bound much less well to a Nef variant containing an engineered F90R mutation that interferes with docking of the native Hck RT-loop. In addition, we could also select RRT-SH3 domains with an opposite specificity, which were dependent on the Arg90 residue for strong binding, and bound 100-fold less well to unmodified Nef. These results demonstrate the utility of phage-display in engineering of signaling protein interaction domains, and emphasize the importance of the RT-loop in SH3 ligand selection, thus suggesting a general strategy for creating SH3 domains with desired binding properties.

L5 ANSWER 27 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:578906 CAPLUS
DOCUMENT NUMBER: 132:92001
TITLE: Combinatorial **peptide libraries** and molecular recognition in T-cell mediated immune response
AUTHOR(S): Fleckenstein, B.; Wiesmuller, K.-H.; Kalbus, M.; Martin, R.; Jung, G.
CORPORATE SOURCE: Institute of Organic Chemistry, University of Tubingen, Tubingen, 72076, Germany
SOURCE: Peptide Science: Present and Future, Proceedings of the International Peptide Symposium, 1st, Kyoto, Nov. 30-Dec. 5, 1997 (1999), Meeting Date 1997, 788-791. Editor(s): Shimonishi, Yasutsugu. Kluwer: Dordrecht, Neth.
CODEN: 68BYA5
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Previously, the authors have studied peptide binding to the MHC class II mols., associated with multiple sclerosis, by applying unadecapeptide amide sublibraries and an activity pattern of the undecapeptide amide library. New DR2b-ligands, from measles virus nucleoprotein were identified and binding was confirmed (Fleckenstein, B., et al., 1996 and 1997). Here, artificial peptide ligands for the TCC (autoreactive human CD4-pos. T cell

clones) 5G7 were designed, just by combining the most effect amino acids with respect to T cell proliferation. These ligands were more potent than myelin basic protein peptide, MBP (86-96) itself, by a factor of 10,000 and more. Screening of protein databases with the library information revealed not only MBP(86-96) as a ligand for TCC 5G7, but also several peptides derived from self and foreign antigens. Thus, based on the Recognition Pattern of TCC 5G7 obtained from screening a combinatorial **peptide library**, about 8 superagonists for TCC 5G7 were identified, but even more than 16 peptide ligands inducing T cell proliferation were discovered. These results underline the value of combinatorial **peptide libraries** for characterizing **peptide** binding to MHC class II mols., resulting in prediction and design of new high-affinity ligands as potential T helper epitopes or antagonists for autoreactive T cells, or possible therapy with respect to tolerance induction.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 95 MEDLINE on STN
ACCESSION NUMBER: 1999348502 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10417390
TITLE: Genetic selection of peptide inhibitors of biological pathways.
AUTHOR: Norman T C; Smith D L; Sorger P K; Drees B L; O'Rourke S M; Hughes T R; Roberts C J; Friend S H; Fields S; Murray A W
CORPORATE SOURCE: Department of Physiology, University of California, San Francisco, CA 94143-0444, USA.. tnorman@microbia.com
CONTRACT NUMBER: P41-RR11823 (NCRR)
SOURCE: Science, (1999 Jul 23) 285 (5427) 591-5.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990820
Last Updated on STN: 20030207
Entered Medline: 19990812

AB Genetic selections were used to find peptides that inhibit biological pathways in budding yeast. The peptides were presented inside cells as peptamers, surface loops on a highly expressed and biologically inert carrier protein, a catalytically inactive derivative of staphylococcal nuclease. Peptamers that inhibited the pheromone signaling pathway, transcriptional silencing, and the spindle checkpoint were isolated. Putative targets for the inhibitors were identified by a combination of two-hybrid analysis and genetic dissection of the target pathways. This analysis identified Ydr517w as a component of the spindle checkpoint and reinforced earlier indications that Ste50 has both positive and negative roles in pheromone signaling. Analysis of transcript arrays showed that the peptamers were highly specific in their effects, which suggests that they may be useful reagents in organisms that lack sophisticated genetics as well as for identifying components of existing biological pathways that are potential targets for drug discovery.

L5 ANSWER 29 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 6
ACCESSION NUMBER: 1999:408430 BIOSIS
DOCUMENT NUMBER: PREV199900408430
TITLE: Identification of residues involved in v-Src substrate recognition by site-directed mutagenesis.
AUTHOR(S): Yokoyama, Noriko; Miller, W. Todd [Reprint author]
CORPORATE SOURCE: Department of Physiology and Biophysics, School of

Medicine, State University of New York, Stony Brook, NY, 11794-8661, USA
SOURCE: FEBS Letters, (Aug. 13, 1999) Vol. 456, No. 3, pp. 403-408. print.
CODEN: FEBLAL. ISSN: 0014-5793.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Oct 1999
Last Updated on STN: 8 Oct 1999

AB To study the role of the catalytic domain in v-Src substrate specificity, we engineered three site-directed mutants (Leu-472 to Tyr or Trp and Thr-429 to Met). The mutant forms of Src were expressed in Sf9 cells and purified. We analyzed the substrate specificities of wild-type v-Src and the mutants using two series of peptides that varied at residues C-terminal to **tyrosine**. The peptides contained either the YMTM motif found in insulin receptor substrate-1 (IRS-1) or the YGEF motif identified from **peptide library** experiments to be the optimal sequence for Src. Mutations at positions Leu-472 or Thr-429 caused changes in substrate specificity at positions P+1 and P+3 (i.e. one or three residues C-terminal to **tyrosine**). This was particularly evident in the case of the L-472W mutant, which had pronounced alterations in its preferences at the P+1 position. The results suggest that residue Leu-472 plays a role in P+1 substrate recognition by Src. We discuss the results in the light of recentwork on the roles of the SH2, SH3 and catalytic domains of Src in substrate specificity.

L5 ANSWER 30 OF 95 MEDLINE on STN
ACCESSION NUMBER: 1999373112 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10441393
TITLE: Benzodiazepine compounds as inhibitors of the src protein **tyrosine kinase**: screening of a combinatorial library of 1,4-benzodiazepines.
AUTHOR: Ramdas L; Bunnin B A; Plunkett M J; Sun G; Ellman J; Gallick G; Budde R J
CORPORATE SOURCE: Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, 77030, USA.
CONTRACT NUMBER: CA16672 (NCI)
CA53617 (NCI)
CA65527 (NCI)
SOURCE: Archives of biochemistry and biophysics, (1999 Aug 15) 368 (2) 394-400.
Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990925
Last Updated on STN: 20000303
Entered Medline: 19990909

AB We screened 1680 spatially separated compounds of a diverse combinatorial library of 1,4-benzodiazepines for their ability to inhibit the **kinase** activity of protein **tyrosine** kinases Src, Yes, Abl, Lck, Csk, and fibroblast growth factor receptor. This screening yielded novel ligands for the protein **tyrosine kinase** Src. In the 1, 4-benzodiazepine-2-one scaffold, the preferred substituent at position R(1) was 4-hydroxyphenylmethyl or a 3-indolemethyl derived from a **tyrosine** or tyrptophan used in building the benzodiazepine, while the substituent at R(2), introduced by alkylating agents, was preferably aromatic in nature. The preferred ring structure introduced on the bicyclic ring of the scaffold by acid chlorides was a

p-hydroxy phenyl group. The lead compound, designated as N-L-Yaa, has a L-4-hydroxyphenylmethyl ring at R(1) and a biphenylmethyl substituent at R(2). The compound has an IC(50) of 73 microM against Src, 2- to 6-fold lower than against other protein **tyrosine** kinases and >10-fold lower than against other nucleotide-utilizing enzymes. The mechanism of binding of N-L-Yaa to Src is mixed against the peptidic substrate with a K(i) of 35 microM and noncompetitive against ATP-Mg with a K(i) of 17 microM. Multiple inhibition analysis of the lead compound in the presence of other competitive inhibitors demonstrated that the binding of the lead compound is nonexclusive to the other competitive inhibitor. The inhibitor was found to be nontoxic to the AFB-13-human fibroblasts cells and inhibited the colony formation of HT-29 colon adenocarcinoma cells that are dependent on Src activity.

L5 ANSWER 31 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 7

ACCESSION NUMBER: 1999:526186 BIOSIS
DOCUMENT NUMBER: PREV199900526186
TITLE: p56lck SH2 domain binding motifs from bead binding screening of **peptide libraries** containing phosphotyrosine surrogates.
AUTHOR(S): Broadbridge, Robert J.; Sharma, Ram P. [Reprint author]
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, School of Biological Sciences, University of Southampton, Bassett Crescent East, Southampton, SO16 7PX, UK
SOURCE: Letters in Peptide Science, (Sept., 1999) Vol. 6, No. 5-6, pp. 335-341. print.
ISSN: 0929-5666.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1999
Last Updated on STN: 10 Dec 1999

AB Phosphorylation reactions are key mediators in a variety of biochemical signal processes. Research into the selective inhibition of protein **tyrosine** kinases to generate anticancer agents has made O-phosphotyrosyl analogues important pharmacological tools. The simple procedures reported here involving the formation of iterative **peptide libraries** together with the development of a selective and sensitive bead-binding assay have made it possible to rapidly screen peptides incorporating O-phosphotyrosyl surrogates (including O-phospho-2,3,5,6-tetrafluorotyrosine, 4-(phosphono)hydroxymethyl-phenylalanine and 4-(phosphono)fluoromethyl-phenylalanine) for their potential to inhibit the protein **tyrosine kinase** p56lck. These procedures can be easily adapted to combinatorial **peptide libraries**.

L5 ANSWER 32 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999343909 EMBASE
TITLE: New antitumor leads from a peptidomimetic library.
AUTHOR: Orfi L.; Waczek F.; Kovesdi I.; Meszaros G.; Idei M.; Horvath A.; Hollosy F.; Mak M.; Szegedi Z.; Szende B.; Keri G.
CORPORATE SOURCE: G. Keri, Peptide Biochemistry Research Group, Department of Medical Chemistry, Semmelweis University of Medicine, 10 P.O. Box 260, H-1444 Budapest, Hungary. keri@puskin.sote.hu
SOURCE: Letters in Peptide Science, (1999) Vol. 6, No. 5-6, pp. 325-333.
Refs: 22
ISSN: 0929-5666 CODEN: LPSCEM
COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19991021
Last Updated on STN: 19991021

AB A parallel combinatorial library of over 1600 compounds has been designed and synthesized for the development of new potential peptidomimetic protein **tyrosine kinase** (PTK) inhibitor leads. These peptidomimetic molecules are aimed at intervening with the substrate binding site of the pp60(c-src) enzyme. The new structures were based on known PTK inhibitors with at least two variously substituted aromatic moieties attached by spacer groups of different length and flexibility. Eleven bis-aryl-type inhibitory compounds were found in the range of 18-100 μM IC50 concentrations from combinations of 12 different substituents. Molecular modeling of the active compounds showed a characteristic distance of 12-14 Å between the farthest sp2 carbon atoms of the two aromatic rings. Conformational analysis of several peptide substrates recently found for pp60(c-src) PTK showed that the energy- minimized conformers had the same distance between the two aromatic moieties. Several compounds in the library not only showed remarkable PTK inhibitory activity but also a significant apoptosis-inducing effect on HT-29 human colon tumor cells.

L5 ANSWER 33 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:403057 CAPLUS
DOCUMENT NUMBER: 131:270142
TITLE: ATM and lymphoid malignancies; use of oriented **peptide libraries** to identify novel substrates of ATM critical in downstream signaling pathways
AUTHOR(S): Rathbun, G. A.; Ziv, Y.; Lai, J. H.; Hill, D.; Abraham, R. H.; Shiloh, Y.; Cantley, L. C.
CORPORATE SOURCE: Center for Blood Research, Harvard Medical School, Boston, MA, USA
SOURCE: Current Topics in Microbiology and Immunology (1999), 246(Mechanisms of B Cell Neoplasia 1998), 267-274
CODEN: CTMIA3; ISSN: 0070-217X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 25 refs. with some new data on the roles of ATM in normal development and loss of ATM in malignant transformation of lymphoid cells in ataxia telangiectasia. To understand the critical roles of ATM important for normal development, cell cycle control and prevention of malignancies, a relevant approach is dissection of ATM-directed signaling pathways. Recently, several studies have shown that ATM is a **tyrosine kinase**, making it highly likely that this activity is intimately associated with signaling functions of ATM. The authors therefore assayed degenerate, oriented **peptide libraries** to identify substrates of ATM protein **kinase** activity. This method takes advantage of the recognition that protein **kinase** catalytic clefts generally recognize primary amino acid sequences around a fixed phosphorylation site.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 34 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:44909 CAPLUS
DOCUMENT NUMBER: 132:279504
TITLE: Design and synthesis of novel src homology-2 domain

inhibitors
AUTHOR(S): Broadbridge, Robert J.; Sharma, Ram P.; Akhtar, M.
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, University of Southampton, Southampton, SO16 7PX, UK
SOURCE: Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries: Peptides, Proteins and Nucleic Acids--Small Molecule Organic Chemical Diversity, Collected Papers, International Symposium, 5th, London, Sept. 2-6, 1997 (1999), Meeting Date 1997, 211-216. Editor(s): Epton, Roger. Mayflower Scientific Ltd.: Kingswinford, UK.
CODEN: 68OEAA
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report. Phosphotyrosine **peptide libraries** containing urea bonds were synthesized and screened for inhibitory activity against the SH2 domain of **tyrosine kinase** p56lck.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 35 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:396431 CAPLUS
DOCUMENT NUMBER: 131:185233
TITLE: Synthesis and application of **tyrosine kinase** substrate libraries
AUTHOR(S): Zheng, Song; Cummings, Richard; Cubbon, Rose; Park, Young-Whan; Cameron, Patricia; Griffin, Patrick; Hermes, Jeffrey
CORPORATE SOURCE: Dept. of Molecular Design & Diversity, Merck and Co, Inc., Rahway, NJ, 07065-0900, USA
SOURCE: Peptides: Frontiers of Peptide Science, Proceedings of the American Peptide Symposium, 15th, Nashville, June 14-19, 1997 (1999), Meeting Date 1997, 65-66. Editor(s): Tam, James P.; Kaumaya, Pravin T. P. Kluwer: Dordrecht, Neth.
CODEN: 67UCAR
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report on **kinase** assays which utilizes the power of the combinatorial approach while allowing identification of the optimal residues through standard enzymic assays.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 36 OF 95 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1999349457 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10420972
TITLE: Phage display in proteolysis and signal transduction.
AUTHOR: Gram H
CORPORATE SOURCE: Novartis Pharma AG, Arthritis and Bone Metabolism, Basel, Switzerland.
SOURCE: Combinatorial chemistry & high throughput screening, (1999 Feb) 2 (1) 19-28. Ref: 61
Journal code: 9810948. ISSN: 1386-2073.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827

Last Updated on STN: 19990827
Entered Medline: 19990818

AB The power of the phage display technology relies on the coupling of the functional display of combinatorial **peptide** or protein **libraries** with the ability of each member in the library to self-replicate and, at the same time, to encode the primary structure of the displayed polypeptide in its genome. Phage display systems, therefore, reflect the principle of encoded combinatorial chemistry close to perfection. Phage display libraries have extensively been used for the selection of peptides, antibody combining sites or protein variants binding to given structures such as polypeptides, carbohydrates, nucleic acids or small molecular weight compounds. The use of **peptide libraries** in selecting molecular interaction partners was extensively described in numerous publications and was subject to a variety of review articles in the past. More recently, and in the focus of this review, combinatorial phage libraries have been employed to examine substrate recognition in catalysis and signal transduction. The sensitivity and versatility of phage display for probing molecular recognition and catalysis by enzymes was demonstrated inasmuch as discriminating peptide substrates could be identified for even closely related proteases or **tyrosine** kinases. Furthermore, the modification of whole phage libraries by **tyrosine** kinases led to the identification of phosphopeptides specific for Src-homology-2 (SH2)- and phosphotyrosine-binding (PTB) domains, which are both structural and functional modules facilitating substrate recognition by protein kinases, phosphatases or adapter molecules involved in signal transduction.

L5 ANSWER 37 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1998:184040 CAPLUS
DOCUMENT NUMBER: 128:241245
TITLE: Detection of substrate recognition by protein kinases and phosphatases
INVENTOR(S): Balasubramanian, Shankar; Abell, Christopher
PATENT ASSIGNEE(S): Cambridge University Technical Services Ltd., UK; Balasubramanian, Shankar; Abell, Christopher
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9811251	A1	19980319	WO 1997-GB2466	19970910
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9741314	A1	19980402	AU 1997-41314	19970910
PRIORITY APPLN. INFO.:			GB 1996-19168 A	19960913
			WO 1997-GB2466 W	19970910

AB A novel assay system is provided that can be utilized to screen a resin-bound or solution-phase phosphotyrosine **peptide library** for substrate turnover by a selected protein **tyrosine** phosphatase (PTP) or **kinase**. The basis of this invention is the discovery that a **tyrosine**-containing peptide is a good substrate for α-chymotrypsin, whereas the analogous

phosphotyrosyl peptide is not. Thus, a library of phosphotyrosyl peptides is screened with a phosphatase. Those phosphopeptides which are substrates for the phosphatase will be dephosphorylated, converting the phosphotyrosine to **tyrosine**. The library is then treated with a second enzyme, chymotrypsin, which leaves the phosphopeptides unchanged, but cleaves those peptides which (as phosphopeptides) were substrates for the phosphatase. Cleavage of the peptide can be detected in several ways known to the art. This system may be extended for screening kinases by running them in the reverse direction (i.e., as phosphatases). This can be achieved by treating the phosphotyrosine **peptide library** with a protein **tyrosine kinase** and ADP or water, under conditions where the **kinase** reaction operates in the reverse direction, to dephosphorylate the phosphopeptide and also form ATP or phosphate. After treatment with chymotrypsin, any cleaved dephosphorylated peptides would be detected as described for the protein **tyrosine** phosphatase assay. The assay is demonstrated using the substrate specificity of leukocyte antigen receptor (LAR) phosphatase where the undecapeptide corresponding to the autophosphorylation site of the epidermal growth factor is used as a prototype sequence for the combinatorial library.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 38 OF 95 MEDLINE on STN

ACCESSION NUMBER: 1998254535 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9585562
TITLE: Studying receptor-ligand interactions using encoded amino acid scanning.
AUTHOR: Camarero J A; Ayers B; Muir T W
CORPORATE SOURCE: Laboratory of Synthetic Protein Chemistry, The Rockefeller University, New York 10021, USA.
CONTRACT NUMBER: GM55843-01 (NIGMS)
SOURCE: Biochemistry, (1998 May 19) 37 (20) 7487-95.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980708
Last Updated on STN: 20020420
Entered Medline: 19980622

AB A novel technique is described that allows the synthesis, functional analysis, and quantitative readout of defined arrays of polypeptide analogues in aqueous solution. Key to this approach is the use of a simple encoding-decoding system in which a unique Fmoc-amino acid tag is covalently attached to the C terminus of each member of a molecular array through a selectively cleavable bond. These tags can be cleanly removed from the molecules they encode, allowing single-step characterization and quantification of the entire mixture by HPLC. The utility of this technique is illustrated through the preparation of an array of proline-rich sequences based on the exchange factor C3G, one of the natural ligands of the N-terminal SH3 domain from the proto-oncogene, c-Crk. The array was designed to systematically modify those residues within the C3G peptide ligand thought to make key interactions with the c-Crk SH3 domain. Using competition binding experiments, it was possible to determine the relative ED50 values for the entire array of molecules simultaneously. These studies revealed that in order to maintain optimal binding to the SH3 domain, the P-3 side chain of the ligand must be positively charged and the P-0 side chain must be hydrophobic and extend beyond the gamma-carbon. The excellent correlation between these relative ED50 values and a series of relative Kd values determined from individual

peptides suggests that this approach may be useful in determining, in a parallel fashion, the relative biological activities of arrays of polypeptides.

L5 ANSWER 39 OF 95 MEDLINE on STN
ACCESSION NUMBER: 1998283404 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9622085
TITLE: Peptides derived from self-proteins as partial agonists and antagonists of human CD8+ T-cell clones reactive to melanoma/melanocyte epitope MART1(27-35).
AUTHOR: Loftus D J; Squarcina P; Nielsen M B; Geisler C; Castelli C; Odum N; Appella E; Parmiani G; Rivoltini L
CORPORATE SOURCE: Laboratory of Cell Biology, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA.
SOURCE: Cancer research, (1998 Jun 1) 58 (11) 2433-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 19980716
Entered Medline: 19980707

AB The self-peptide MART1(27-35) derives from the melanocyte/melanoma protein Melan A/MART1 and is a target epitope of CD8+ T cells, commonly recovered from tumor-infiltrating lymphocytes of HLA-A2.1+ melanoma patients. Despite their prevalence in such patients, these CTLs generally appear to be ineffective in mediating tumor regression in vivo. We have noted previously that numerous peptides from both endogenous and foreign proteins are similar to MART1(27-35) and, potentially, are capable of productively engaging the T-cell receptors of patient-derived CTLs. This observation raised the question of whether CTLs in vivo might encounter self-peptide analogues of MART1(27-35) that lack full agonist activity, perhaps to the detriment of the antitumor CTL response. This possibility was evaluated using cloned, patient-derived CTLs with a panel of self-derived natural analogues of MART1(27-35) in assays for cytolysis, cytokine release, and phosphorylation of T-cell receptor signaling constituents. Several peptides were identified as partial agonists, capable of eliciting cytolysis and/or release of cytokines tumor necrosis factor-alpha and IFN-gamma but not interleukin 2. Several other peptides showed antagonist behavior, effectively inhibiting cytolysis of MART1(27-35)-pulsed targets, but did not inhibit killing of cells prepulsed with a synthetic, heteroclitic variant of MART1(27-35). Some of these antagonists also had lasting effects on interleukin 2 secretion by CTLs under experimental conditions involving sequential exposure to ligands. Together, these observations suggest that encounters with self-peptide analogues of MART1(27-35) may contribute to the peripheral maintenance of these CTLs, while ultimately impairing the efficacy of this antitumor T-cell response.

L5 ANSWER 40 OF 95 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 1999090214 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9873528
TITLE: Comparison of the intrinsic **kinase** activity and substrate specificity of c-Abl and Bcr-Abl.
AUTHOR: Wu J J; Phan H; Lam K S
CORPORATE SOURCE: Selectide Corporation, A Subsidiary of Hoechst Marion Roussel, Inc., Tucson, AZ 85737, USA.
SOURCE: Bioorganic & medicinal chemistry letters, (1998 Sep 8) 8 (17) 2279-84.
Journal code: 9107377. ISSN: 0960-894X.

PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990216
Last Updated on STN: 19990216
Entered Medline: 19990201

AB We studied the intrinsic **tyrosine kinase** activity and substrate specificity of c-Abl and Bcr-Abl protein **tyrosine** kinases (PTKs) using the peptide substrates discovered from a synthetic combinatorial **peptide library**. Our data indicate that the phosphorylation of these peptides by Bcr-Abl was consistently stronger than that by c-Abl. Bcr-Abl also showed substrate preference towards those peptides with one or more positive charges.

L5 ANSWER 41 OF 95 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 1998244538 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9585139
TITLE: Application of "one-bead one-compound" combinatorial library methods in signal transduction research.
AUTHOR: Lam K S; Sroka T; Chen M L; Zhao Y; Lou Q; Wu J; Zhao Z G
CORPORATE SOURCE: Arizona Cancer Center, Department of Medicine, College of Medicine, University of Arizona, Tucson 85724-5024, USA.
CONTRACT NUMBER: CA17094 (NCI)
CA23074 (NCI)
CA57723 (NCI)
SOURCE: Life sciences, (1998) 62 (17-18) 1577-83.
Journal code: 0375521. ISSN: 0024-3205.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980526

AB Using a "split-synthesis" solid phase synthetic approach, bead libraries can be generated such that each bead displays only one chemical entity. This "one-bead one-compound" combinatorial library can then be assayed for specific biological properties using either a solid-phase on-bead binding or functional assay, or a releasable solution phase assay. Positive compound-beads can then be isolated for structure determination. Various assay systems to screen such a "one-bead one-compound" library are described. We have used this combinatorial library method to discover peptides that bind to the cell surface immunoglobulins of murine lymphoma cells. Such peptides, when presented in an oligomeric form to a lymphoma cell are able to induce signal transduction. Additionally, we have also applied the "one-bead one-compound" combinatory **library** approach to elucidate **peptide** substrate motifs for protein **tyrosine** kinases. Multiple distinct peptide motifs were identified for p60(c-src) protein **tyrosine kinase**. Using the identified peptide substrates as templates, potent and highly specific pseudosubstrate-based peptide inhibitors were developed.

L5 ANSWER 42 OF 95 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 1998285233 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9623775
TITLE: Signal transduction by the peptide which mimics the activity of thrombopoietin.
AUTHOR: Kimura T; Kaburaki H; Tsujino T; Watanabe Y; Kato H
CORPORATE SOURCE: Research and Development Division, Hokuriku Seiyaku Co.,

Ltd., Katsuyama, Fukui, Japan.
SOURCE: Biochemistry and molecular biology international, (1998 May) 44 (6) 1203-9.
Journal code: 9306673. ISSN: 1039-9712.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980812

AB Thrombopoietin (TPO) plays a central role in megakaryopoiesis and platelet production. It is a ligand for c-mpl, which is a member of the hematopoietic receptor superfamily. We have recently identified several human c-mpl binding peptides which are distinct from TPO, from phage random **peptide libraries**. PK1M is one of these peptides and is an agonist of c-mpl which is TPO receptor. We show here that PK1M induces the **tyrosine** phosphorylation of the Janus **kinase** 2 (JAK2) and the activation of the signal transducer and activation of transcription 5 (STAT5) in TPO-dependent cells like TPO.

L5 ANSWER 43 OF 95 MEDLINE on STN
ACCESSION NUMBER: 1999088753 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9871587
TITLE: Solid phase synthesis of a biased mini tetrapeptoid-library for the discovery of monodentate ITAM mimics as ZAP-70 inhibitors.
AUTHOR: Revesz L; Bonne F; Manning U; Zuber J F
CORPORATE SOURCE: Preclinical Research Novartis, Basel, Switzerland.. laszlo.revesz@pharma.novartis.com
SOURCE: Bioorganic & medicinal chemistry letters, (1998 Mar 3) 8 (5) 405-8.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990114

AB The biased library was composed of a novel phosphotyrosine mimic fixed in the P1 position of a tetrapeptoid and combined with three lipophilic N-substituents at the remaining positions giving a total of 27 single compounds. Screening for ZAP-70 antagonism identified 8 as a novel selective monodentate ZAP-70 antagonist and lead in the search for new immunosuppressive drugs.

L5 ANSWER 44 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:3225 CAPLUS
DOCUMENT NUMBER: 130:181193
TITLE: Characterization of antigen-antibody interactions using single substitution analogs and mixture-based synthetic combinatorial libraries
AUTHOR(S): Appel, J. R.; Campbell, G. D.; Buencamino, J.; Houghten, R. A.; Pinilla, C.
CORPORATE SOURCE: Torrey Pines Institute for Molecular Studies, San Diego, CA, 92121, USA
SOURCE: Journal of Peptide Research (1998), 52(5), 346-355
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Munksgaard International Publishers Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English

AB In an effort to use monoclonal antibodies (mAbs) as selective probes for early detection of breast cancer, the specificities of a number of antipeptide mAbs have been studied at the individual amino acid level using single substitution **peptide** analogs and **peptide** combinatorial **libraries**. In this study, the mapping results are presented for mAb 172-12A4, which was raised against the haptenic peptide LGSGAFGTIYKG(C), corresponding to residues 138-149 of the oncogene v-erbB. This peptide is homologous with a region in epidermal growth factor receptor (EGFR) and human oncogene c-erbB-2, and contains the ATP binding motif that is common among protein kinases. The substitution profile of this interaction correlated well with the results from the screening of hexa- and decapeptide positional scanning libraries. Based on the results of this mAb's specificity for the antigenic determinant (-AFGTIYK-), proteins that have sequence homol. were found from a database search of human sequences. Thirty-two unique peptide sequences, a majority of which was from protein kinases, were synthesized and tested for recognition by mAb 172-12A4. Eleven peptides had activities that differed from the original peptide by less than an order of magnitude, and the activities for 29 of the 32 (90%) could be accurately predicted based on the individual substitution analog results. While both epitope mapping approaches address the amino acid level of mAb specificity, positional scanning libraries offer an advantage of identifying the positional importance of each antigenic determinant residue without any prior knowledge of the mAb's specificity. The fine specificity mapping of peptide-specific mAbs using the synthetic tools illustrated here will be useful for the development of immunodiagnostics that detect cancer-related proteins in clin. samples.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 45 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1998394517 EMBASE
TITLE: Src Homology-2 Domains: Structure, mechanisms, and drug discovery.
AUTHOR: Sawyer T.K.
CORPORATE SOURCE: T.K. Sawyer, ARIAD Pharmaceuticals, Inc., 26 Landsdowne St., Cambridge, MA 02139, United States.
tomi.sawyer@ariad.com
SOURCE: Biopolymers - Peptide Science Section, (1998) Vol. 47, No. 3, pp. 243-261.
Refs: 44
ISSN: 0006-3525 CODEN: BPSSFT
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19981210
Last Updated on STN: 19981210

AB Src homology-2 (SH2) domains and their associated catalytic or noncatalytic proteins constitute critical signal transduction targets for drug discovery. Such SH2 proteins are found in the regulation of a number of cellular processes, including growth, mitogenesis, motility, metabolism, immune response, and gene transcription. From the relationship of **tyrosine** phosphorylation and intracellular regulation by protein-**tyrosine** kinases (PTKs) and protein-**tyrosine** phosphatases (PTPs), the dynamic and reversible binding interactions of SH2 domain containing proteins with their cognate

phosphotyrosine (pTyr) containing proteins provide a third dimensionality to the orchestration of signal transduction pathways that exist as a result of pTyr formation, degradation, and molecular recognition events. This review highlights several key research achievements impracting our current understanding of SH2 structure, mechanisms, and drug discovery that underlie the role(s) of SH2 domains in signal transduction processes, cellular functions, and disease states.

L5 ANSWER 46 OF 95 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 1999033813 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9817025
TITLE: Protein **tyrosine** kinases: structure, substrate specificity, and drug discovery.
AUTHOR: al-Obeidi F A; Wu J J; Lam K S
CORPORATE SOURCE: Selectide Corporation, A Subsidiary of Hoechst Marion Roussel, Inc., Tucson, AZ 85737, USA.
SOURCE: Biopolymers, (1998) 47 (3) 197-223. Ref: 198
Journal code: 0372525. ISSN: 0006-3525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981202

AB Protein **tyrosine** kinases (PTKs) play a crucial role in many cell regulatory processes. It is therefore not surprising to see that functional perturbation of PTKs results in many diseases. Despite the diverse primary structure organization of various PTKs, the catalytic or **kinase** domains of various PTKs as well as that of Ser/Thr kinases are generally conserved. The high resolution crystal structure of a few PTKs has been solved in the last few years. In contrast to the well-defined linear peptide substrate motifs recognized by specific Ser/Thr kinases, the identification of specific substrate motifs for PTK has been slow. It is not until recently that through the use of combinatorial **peptide library** methods that specific recognition motifs for specific PTKs have begun to emerge. Efficient and specific peptide substrates for some PTKs with Km at the mid microM range have been identified. Based on these peptide substrates, relatively potent (IC50 at the low microM range) and highly selective pseudosubstrate-based peptide inhibitors have been developed. There has been enormous effort in the development of PTK inhibitors for diseases such as cancer, psoriasis, and osteoporosis. Several new high-throughput PTK assay technologies have recently been described. Small molecules against specific PTK have been developed. Most of them are competitive inhibitors at the ATP binding site. Some of these inhibitors have already been in clinical trial.

L5 ANSWER 47 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1998394514 EMBASE
TITLE: 'Signal transduction targets: Structure, mechanisms, and drug discovery'. Editorial.
AUTHOR: Sawyer T.K.
CORPORATE SOURCE: T.K. Sawyer, ARIAD Pharmaceuticals, 26 Landsclowne Street, Cambridge, MA 02139, United States
SOURCE: Biopolymers - Peptide Science Section, (1998) Vol. 47, No. 3, pp. 195.
ISSN: 0006-3525 CODEN: BPSSFT
COUNTRY: United States

DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 19981210
Last Updated on STN: 19981210
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L5 ANSWER 48 OF 95 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 1998087674 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9425036
TITLE: Peptide and protein phosphorylation by protein **tyrosine kinase** Csk: insights into specificity and mechanism.
AUTHOR: Sondhi D; Xu W; Songyang Z; Eck M J; Cole P A
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, The Rockefeller University, New York 10021, USA.
CONTRACT NUMBER: CA74305-01 (NCI)
SOURCE: Biochemistry, (1998 Jan 6) 37 (1) 165-72.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980202

AB Csk (C-terminal Src **kinase**) is a protein **tyrosine kinase** that phosphorylates Src family member C-terminal tails, resulting in down-regulation of Src family members. The molecular basis of Csk's substrate specificity and catalytic mechanism with a protein substrate was investigated. Using a **peptide library** approach, preferential amino acids which are unrelated to the conserved Src C-terminal sequence were identified. The validity of these preferences was confirmed by synthesizing a short consensus peptide and demonstrating its high catalytic efficiency with Csk. These results underscore the difficulties of relying on amino acids neighboring **tyrosine** in protein sequences as predictors of protein **kinase** substrate specificity for in vivo analysis. In addition, a catalytically inactive version of the Src family member, Lck (lymphoid cell **kinase**), was expressed, purified, and evaluated as a Csk substrate. It was proven to be the most catalytically efficient substrate yet identified for Csk. The high efficiency of purified Csk phosphorylating a pure, unphosphorylated Src family member argues against the importance of an SH2-phosphotyrosine docking interaction or the involvement of extra recruitment proteins in facilitating Csk phosphorylation of Src family members. Kinetic studies revealed that the chemical step is at least partially rate-determining in Csk-mediated phosphoryl transfer to the Lck protein. Other properties including preferences for Mn over Mg, thio effects, and Km's for ATP also correlate fairly well between protein and peptide phosphorylation. The lack of a significant impact of increased salt on the Km for Lck phosphorylation differs from Csk-mediated poly(Glu,Tyr) phosphorylation, and argues against the importance of electrostatic effects in the Csk-Lck binding interaction. The failure of the Lck phosphorylation product (phosphotyrosine-505) to significantly inhibit Csk phosphorylation of Lck is consistent with a catalytic model involving multidomain structural interactions between substrate and enzyme.

L5 ANSWER 49 OF 95 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 1998330871 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9666442
TITLE: Use of **peptide libraries** to determine optimal substrates of **tyrosine** kinases.
AUTHOR: Chan P M; Miller W T
CORPORATE SOURCE: Department of Physiology and Biophysics, State University of New York at Stony Brook, USA.
SOURCE: Methods in molecular biology (Clifton, N.J.), (1998) 84 75-86.
Journal code: 9214969. ISSN: 1064-3745.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981006

L5 ANSWER 50 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:440824 CAPLUS
DOCUMENT NUMBER: 129:211222
TITLE: Application of the one-bead one-compound combinatorial library method in protein **tyrosine kinase** and cell surface receptor research
AUTHOR(S): Lam, K. S.; Lou, Q.; Wu, J.; Leftwich, M.; Mckay, R. T.; Rychetsky, L.; Phan, H.; Joe, J.; Chen, M. -L.; Liu-Stevens, R.; Zhao, Y.; Salmon, S. E.
CORPORATE SOURCE: Arizona Cancer Center, Department of Medicine, University of Arizona, Tucson, AZ, 85724, USA
SOURCE: Peptides: Biology and Chemistry, Proceedings of the Chinese Peptide Symposium, 4th, Chengdu, Peop. Rep. China, July 21-25, 1996 (1998), Meeting Date 1996, 55-58. Editor(s): Xu, Xiao-Jie; Ye, Yun-Hua; Tam, James P. Kluwer: Dordrecht, Neth.
CODEN: 66KJAP
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The "one-bead one-compound" combinatorial library method is extremely versatile and can be used to discover ligands for various mol. targets. Assays can be developed such that a specific biol. or phys. property can be detected. These assays, whether on-bead or in solution phase can easily be adapted to the "one-bead one-compound" library concept in e.g. protein **tyrosine kinase** and cell surface receptor research.
Thus far, this specific combinatorial library method has proven to be very useful in both basic research and drug discovery.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 51 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:62641 CAPLUS
DOCUMENT NUMBER: 128:125194
TITLE: Exploring the Specificity Pockets of Two Homologous SH3 Domains Using Structure-Based, Split-Pool Synthesis and Affinity-Based Selection
AUTHOR(S): Kapoor, Tarun M.; Andreotti, Amy Hamilton; Schreiber, Stuart L.
CORPORATE SOURCE: Department of Chemistry and Chemical Biology Howard Hughes Medical Institute, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Journal of the American Chemical Society (1998), 120(1), 23-29
CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Split-pool synthesis was used to prepare large nos. of spatially-separated mols.
and thereby to investigate the specificity pockets of similar SH3 domains found in the **tyrosine** kinases Src and Hck. By taking into account the structure of the Src SH3 domain complexed to a ligand containing non-peptide-binding elements, the mols. were designed to complement the topog. of the protein's binding pocket. This procedure led to the discovery of ligands having greater affinity and enhanced selectivity for the Src SH3 domain. It also yielded non-natural ligands that bind selectively to the Hck SH3 domain. Insights gained from this strategy may facilitate the discovery of mols. useful for evaluating the cellular function of SH3-domain-containing proteins.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 52 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:238383 CAPLUS
DOCUMENT NUMBER: 126:289598
TITLE: L-Dopa: A Powerful Nonphosphorylatable **Tyrosine** Mimetic for pp60c-src
AUTHOR(S): Niu, Jinkui; Lawrence, David S.
CORPORATE SOURCE: Department of Biochemistry Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, 10461-1602, USA
SOURCE: Journal of the American Chemical Society (1997), 119(16), 3844-3845
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB L-Dopa-substituted peptide is a significantly more potent inhibitor of pp60c-src than the corresponding phenylalanine derivative The inhibitory trends observed with C-terminus-substituted peptides may hold more conventional peptidic environments. In order to address this question the peptides Glu-Glu-Leu-Leu-Phe-Gly-Glu-Ile (I) and Glu-Glu-Leu-Leu-L-Dopa-Gly-Glu-Ile (II) were prepared The primary sequence encompassing the Phe and L-Dopa residues was chosen, in part, from the results of a previous study using a combinatorial **peptide library** to assess pp60c-src-specificity. II is a 33-fold more effective inhibitor than I. Furthermore, both peptides are competitive inhibitors vs. peptide substrate (see Supporting Information). Indeed, the difference in Ki values exhibited by I and II is even more substantial (55-fold) than that observed for the corresponding IC50s. Finally, since the L-Dopa-containing peptide serves as a noncompetitive inhibitor vs. variable ATP, it is evident that this inhibitory species does not coordinate to the ATP binding site. We failed to detect a time-dependent inactivation of pp60c-src in the presence of II that is any more substantial than in the absence of the peptide i.e., a slight, yet identical, loss in **tyrosine kinase** activity as a function of time is observed in both the presence and absence of II. Consequently, we conclude that the L-Dopa-containing peptide only serves as a simple reversible inhibitor of pp60c-src.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 53 OF 95 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 97301578 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9157979
TITLE: Potent pseudosubstrate-based peptide inhibitors for

p60(c-src) protein **tyrosine kinase**.

AUTHOR: Lou Q; Leftwich M E; McKay R T; Salmon S E; Rychetsky L; Lam K S

CORPORATE SOURCE: Department of Medicine, Arizona Cancer Center, University of Arizona College of Medicine, Tucson 85724, USA.

CONTRACT NUMBER: CA17094 (NCI)
CA23074 (NCI)
CA57723 (NCI)

SOURCE: Cancer research, (1997 May 15) 57 (10) 1877-81.
Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199706

ENTRY DATE: Entered STN: 19970620
Last Updated on STN: 19970620
Entered Medline: 19970610

AB We recently reported the identification of GIYWHHY as an efficient and specific substrate for p60(c-src) protein **tyrosine kinase** (PTK) by screening a secondary random **peptide library** (Q. Lou et al., Bioorg. Med. Chemical, 4: 677-682, 1996). Based on the primary structure of GIYWHHY, we designed and synthesized several pseudosubstrate-based peptide inhibitors. Some of these peptide inhibitors are highly potent and specific with IC50 in the low micromolar range. Because both YIYGSFK and GIYWHHY are efficient and specific substrates for p60(c-src) PTK, chimeric branched peptides based on these two sequences were synthesized. These branched peptides inhibit p60(c-src) PTK with high potency, indicating that the enzyme-active site of p60(c-src) PTK can accommodate more than a linear motif. This may explain why seemingly several peptides with very different linear structures can all be phosphorylated by this enzyme.

L5 ANSWER 54 OF 95 CAPLUS

ACCESSION NUMBER: 1997:307132 CAPLUS

DOCUMENT NUMBER: 127:16322

TITLE: Identification of high potency microbial and self ligands for a human autoreactive class II-restricted T cell clone

AUTHOR(S): Hemmer, Bernhard; Fleckenstein, Burkhard T.; Vergelli, Marco; Jung, Gunther; Mcfarland, Henry; Martin, Roland; Wiesmuller, Karl-Heinz

CORPORATE SOURCE: Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892-1400, USA

SOURCE: Journal of Experimental Medicine (1997), 185(9), 1651-1659
CODEN: JEMEAV; ISSN: 0022-1007

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB CD4+ class II-restricted T cells specific for self antigens are thought to be involved in the pathogenesis of most human autoimmune diseases and mol. mimicry between foreign and self ligands has been implicated as a possible mechanism for their activation. In this report the authors introduce combinatorial **peptide libraries** as a powerful tool to identify cross-reactive ligands for these T cells. The antigen recognition of a CD4+ T cell clone (TCC) specific for myelin basic protein peptide (MBP) (86-96) was dissected by the response to a set of 220 11-mer peptide sublibraries. Based on the results obtained with the libraries for each position of the antigen, artificial peptides were found that induced proliferative responses at much lower concns. than MBP(86-96). In

addition stimulatory ligands derived from protein sequences of self and microbial proteins were identified, some of them even more potent agonists than MBP(86-96). These results indicate that: (a) for at least some autoreactive CD4+ T cells antigen recognition is highly degenerate; (b) the autoantigen used to establish the TCC represents only a suboptimal ligand for the TCC; (c) a completely random and unbiased approach such as combinatorial **peptide libraries** can decrypt the spectrum of stimulatory ligands for a T cell receptor (TCR).

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 55 OF 95 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 97366804 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9223634
TITLE: Modified phage **peptide libraries** as a tool to study specificity of phosphorylation and recognition of **tyrosine** containing peptides.
AUTHOR: Dente L; Vetriani C; Zucconi A; Pelicci G; Lanfrancone L; Pelicci P G; Cesareni G
CORPORATE SOURCE: Dipartimento di Biologia Universita di Roma Tor Vergata, Rome, Italy.
SOURCE: Journal of molecular biology, (1997 Jun 27) 269 (5) 694-703.
Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970825
Last Updated on STN: 19970825
Entered Medline: 19970813

AB **Tyrosine** phosphorylation and protein recognition, mediated by phosphotyrosine containing peptides, play an important role in determining the specific response of a cell, when stimulated by external signals. We have used peptide repertoires displayed by filamentous phage as a tool to study the substrate specificity of the protein **tyrosine kinase** (PTK) p55(fyn) (Fyn). **Peptide libraries** were incubated for a short time in the presence of Fyn and phages displaying efficiently phosphorylated peptides were selected by panning over anti-phosphotyrosine antibodies. The characterization of the peptides enriched after three phosphorylation/selection rounds allowed us to define a canonical substrate sequence for the **kinase** Fyn, E-(phi/T)YGx phi, where phi represents any hydrophobic residue. A peptide conforming to this sequence is a better substrate than a second peptide designed to be in accord with the consensus sequence recognised by the Fyn SH2 domain. When the library phosphorylation reaction is carried out in saturation conditions, practically all the **tyrosine** containing peptides are phosphorylated, irrespective of their context. These "fully modified" **peptide libraries** are a valuable tool to study the specificity of phosphotyrosine mediated protein recognition. We have used this new tool to identify a family of peptides that bind the PTB domain of the adapter protein Shc. Comparison of the peptide sequences permits us to confirm the essential role of N at position -3, while P often found at position -2 in natural targets is not absolutely required. Furthermore, our approach permits us to reveal an "extended" consensus indicating that residues that do not seem to influence binding in natural peptides can make productive contacts, at least in linear peptides.

L5 ANSWER 56 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 18
ACCESSION NUMBER: 1997:339743 BIOSIS

DOCUMENT NUMBER: PREV199799638946
TITLE: Identification of phosphopeptide ligands for the Src-homology 2 (SH2) domain of Grb2 by phage display.
AUTHOR(S): Gram, Hermann [Reprint author]; Schmitz, Rita; Zuber, Jean Francois; Baumann, Gotz
CORPORATE SOURCE: c/o Novartis Pharma A.G., Arthritis Bone Metabolism, Build. 386/927, CH-4002 Basel, Switzerland
SOURCE: European Journal of Biochemistry, (1997) Vol. 246, No. 3, pp. 633-637.
CODEN: EJBCAI. ISSN: 0014-2956.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Aug 1997
Last Updated on STN: 4 Sep 1997

AB We report here on the identification of phosphopeptide ligands which interact with the Src-homology 2 (SH2) domain of the adapter protein Grb2 by screening a random **peptide library** established on phage. Phage were phosphorylated in vitro at an invariant **tyrosine** residue by a mixture of phosphotyrosine kinases c-Src, Blk and Syk. Selection of binding motifs was carried out by interaction of the library with the recombinant SH2 domain of Grb2 expressed as a glutathione S-transferase (GST) fusion protein. Several subsequent cycles of selection led to the enrichment of phage which bound to the GST-Grb2 SH2 domain only when previously phosphorylated. Sequence analysis revealed that all of the selected phage displayed peptides with the consensus motif Y*M/ENW (Y* denotes phosphotyrosine). One of these peptides, bearing the Y*M/ENW motif, bound the Grb2 SH2 domain with a threefold higher affinity than the peptide motif Y*VNV derived from the natural ligand Shc. Thus, phage display can be employed to rapidly identify high affinity ligands to SH2 domains.

L5 ANSWER 57 OF 95 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 97352540 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9208935
TITLE: Sequence specificity of C-terminal Src **kinase** (CSK)--a comparison with Src-related kinases c-Fgr and Lyn.
AUTHOR: Ruzzene M; Songyang Z; Marin O; Donella-Deana A; Brunati A M; Guerra B; Agostinis P; Cantley L C; Pinna L A
CORPORATE SOURCE: Dipartimento di Chimica Biologica, Universita di Padova, and Centro di Studio delle Biomembrane del Consiglio Nazionale delle Ricerche, Italy.
SOURCE: European journal of biochemistry / FEBS, (1997 Jun 1) 246 (2) 433-9.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970812
Last Updated on STN: 20000303
Entered Medline: 19970728

AB An eicosapeptide encompassing the C-terminal tail of c-Src (Tyr527) which is conserved in most Src-related protein kinases, is phosphorylated by C-terminal Src **kinase** (CSK) and by the two Src-related protein kinases c-Fgr and Lyn, with similar kinetic constants. Two related peptides reproducing the C-terminal segments of c-Src mutants defective in CSK phosphorylation [MacAuley, A., Okada, M., Nada, S., Nakagawa, H. & Cooper, J. A. (1993) Oncogene 8, 117-124] AFLEDSCTGTEPLYQRGENL (mutant number 28) and AFLEDNFTGTKPQYHPGENL (mutant number 29), proved a better and a much worse substrates, respectively than the wild-type peptide, with either CSK or the two Src kinases. By changing individual residues in the

best peptide substrate, it was shown that the main element responsible for its improved phosphorylation is leucine at position -1 (instead of glutamine), while lysine at position -3 (instead of glutamate) has a detrimental effect, possibly accounting for the negligible phosphorylation of peptide derived from mutant number 29. By contrast to most peptide substrates, including the Src C-terminal peptides, which exhibit relatively high K(m) values, a polyoma-virus-middle-T-antigen-(mT)-derived peptide with **tyrosine** embedded in a highly hydrophobic sequence (EEEPQFEEIPIYLELLP) exhibits with CSK a quite low K(m) value (63 microM). Consistent with this, the optimal sequence selected by CSK in an oriented **peptide library** is XXXIYMFFF. This is different from sequences selected by Lyn (DEEIYEELX) and c-Fgr (XEEIYGIFF), although they all share a high selection for a hydrophobic residue at n-1. In sharp contrast, TPKIIB/p38syk, related to the catalytic domain of p72syk, selects acidic residues at nearly all positions, n-1 included. These data support the notion that the features determining the specific phosphorylation of the C-terminal **tyrosine** residue of Src do not reside in the primary structure surrounding the target **tyrosine**. They also show that this site does not entirely fulfil the optimal consensus sequence recognized by CSK, disclosing the possibility that as yet unrecognized CSK targets structurally unrelated to the C-terminal **tyrosine** residue of Src kinases may exist.

L5 ANSWER 58 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 20
ACCESSION NUMBER: 1997:169571 CAPLUS
DOCUMENT NUMBER: 126:274317
TITLE: A study of Src SH2 domain protein-phosphopeptide binding interactions by electrospray ionization mass spectrometry
AUTHOR(S): Loo, Joseph A.; Hu, Peifeng; McConnell, Patrick; Mueller, W. Tom
CORPORATE SOURCE: Division Warner-Lambert Company, Parke-Davis Pharmaceutical Research, Ann Arbor, MI, 48105, USA
SOURCE: Journal of the American Society for Mass Spectrometry (1997), 8(3), 234-243
CODEN: JAMSEF; ISSN: 1044-0305
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The noncovalent binding of various peptide ligands to pp60SRC (Src) SH2 (Src homol. 2) domain protein (12.9 ku) has been used as a model system for development of electrospray ionization mass spectrometry (ESI-MS) as a tool to study noncovalently bound complexes. SH2 motifs in proteins are critical in the signal transduction pathways of the **tyrosine kinase** growth factor receptors and recognize phosphotyrosine-containing proteins and peptides. ESI-MS with a magnetic sector instrument and array detection has been used to detect the protein-peptide complex with low-picomole sensitivity. The relative abundances of the multiply charged ions for the complex formed between Src SH2 protein and several nonphosphorylated and phosphorylated peptides have been compared. The mass spectrometry data correlate well to the measured binding consts. derived from solution-based methods, indicating that the mass spectrometry-based method can be used to assess the affinity of such interactions. Solution-phase equilibrium consts. may be determined by measuring the amount of bound and unbound species as a function of concentration for construction of a Scatchard graph. ESI-MS of a solution containing Src SH2 with a mixture of phosphopeptides showed the expected protein-phosphopeptide complex as the dominant species in the mass spectrum, demonstrating the method's potential for screening mixts. from **peptide libraries**.

L5 ANSWER 59 OF 95 MEDLINE on STN
ACCESSION NUMBER: 97130098 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8974395
TITLE: Recognition of unique carboxyl-terminal motifs by distinct PDZ domains.
AUTHOR: Songyang Z; Fanning A S; Fu C; Xu J; Marfatia S M; Chishti A H; Crompton A; Chan A C; Anderson J M; Cantley L C
CORPORATE SOURCE: Division of Signal Transduction, Beth Israel Hospital, and Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA.
CONTRACT NUMBER: CA66263 (NCI)
DK34989 (NIDDK)
SOURCE: Science, (1997 Jan 3) 275 (5296) 73-7.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970117

AB The oriented **peptide library** technique was used to investigate the peptide-binding specificities of nine PDZ domains. Each PDZ domain selected peptides with hydrophobic residues at the carboxyl terminus. Individual PDZ domains selected unique optimal motifs defined primarily by the carboxyl terminal three to seven residues of the peptides. One family of PDZ domains, including those of the Discs Large protein, selected peptides with the consensus motif Glu-(Ser/Thr)-Xxx-(Val/Ile) (where Xxx represents any amino acid) at the carboxyl terminus. In contrast, another family of PDZ domains, including those of LIN-2, p55, and Tiam-1, selected peptides with hydrophobic or aromatic side chains at the carboxyl terminal three residues. On the basis of crystal structures of the PSD-95-3 PDZ domain, the specificities observed with the **peptide library** can be rationalized.

L5 ANSWER 60 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:609917 CAPLUS
DOCUMENT NUMBER: 125:248492
TITLE: Preparation of peptides and compounds that bind to SH2 (src homology region 2) domains of proteins and methods for their identification
INVENTOR(S): Patel, Dinesh V.; Gordeev, Mikhail F.; Gordon, Eric; Grove, J. Russell; Hart, Charles P.; Kim, Moon H.; Szardenings, Anna Katrin
PATENT ASSIGNEE(S): Affymax Technologies N.V., Neth.
SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9623813	A1	19960808	WO 1996-US1544	19960131

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE,

IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE

AU 9649720 A1 19960821 AU 1996-49720 19960131

PRIORITY APPLN. INFO.: US 1995-382100 A 19950201

WO 1996-US1544 W 19960131

AB SH2-binding peptides comprising a core sequence of amino acids Z7XZ8X (X = a member independently selected from the group consisting of the 20 genetically coded L-amino acids and the stereoisomeric D-amino acids; Z7 = phosphotyrosine or an isostere thereof; Z8 = asparagine or an isostere thereof; the amino acid terminus is acylated; the peptide is less than 14 amino acids; provided that if Z7 is phosphotyrosine and Z8 is asparagine, then the peptide is not GDGZ7XZ8XPLL), which bind to the SH2 domain or domains of various proteins, are prepared These peptides and compds. have application as agonists and antagonists of SH2 domain containing proteins, and as diagnostic or. A library of peptides bound to a solid support, useful for identifying ligands capable of binding to SH2 domains, is also prepared therapeutic agents for the diagnosis or treatment of disease conditions. A method for identifying an SH2-binding peptide comprises contacting the resp. members of a library with an SH2 domain containing protein or SH2 domain fragment and identifying SH2-binding peptides on the basis of a binding affinity of ≤1 + 10-4 M. In particular, a method for treating a disease associated with aberrant cell growth, differentiation, or regulation which is associated with defects in receptor **tyrosine kinase** pathways comprises administering to a patient above peptide in an amount sufficient to partially block or inhibit a cellular signal transduction pathway. Said disease is selected from cancer, developmental and differentiation disease, and insulin-resistant (or non-insulin dependent) diabetes. Thus, a phosphotyrosine-containing **peptide library** on a solid support with the general sequence A-pY-X1-X2-X3-S-V (pY = phosphotyrosine residue, X1 - X3 = Ala, Arg, Asn, Asp, Glu, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Val, Tyr, Trp, Vvl, Nle, etc.) representing 17,576 peptides was prepared and one of the library sequence (ApYLNESV) showed greater affinity for the SH2 domain than did the pos. control sequence (ApYINQSV, residue from the SH2-binding domain of human EGF) (4.5 μM vs. 12 μM).

L5 ANSWER 61 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:623666 CAPLUS

DOCUMENT NUMBER: 125:321369

TITLE: Identification of Itk/Tsk Src homology 3 domain ligands

AUTHOR(S): Bunnell, Stephen C.; Henry, Pamela A.; Kolluri, Rikki; Kirchhausen, Tomas; Rickles, Richard J.; Berg, Leslie J.

CORPORATE SOURCE: Dep. Mol. Cell. Biol., Harvard Univ., Cambridge, MA, 02138, USA

SOURCE: Journal of Biological Chemistry (1996), 271(41), 25646-25656

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The **tyrosine kinase** Itk/Tsk is a T cell specific analog of Btk, the **tyrosine kinase** defective in the human immunodeficiency X-linked agammaglobulinemia and in xid mice. T lymphocytes from Itk-deficient mice are refractory to mitogenic stimuli delivered through the T cell receptor (TCR). To gain insights into the biochem. role of Itk, the binding properties of the Itk SH3 domain were examined An optimal Itk SH3 binding motif was derived by screening biased phage display libraries; peptides based on this motif bound with high affinity and selectivity to the Itk SH3 domain. Initial studies with T cell lysates indicated that the Itk SH3 domain bound Cbl, Fyn, and other

tyrosine phosphoproteins from TCR-stimulated Jurkat cells. Under conditions of increased detergent stringency Sam 68, Wiskott-Aldrich Syndrome protein, and hnRNP-K, but not Cbl and Fyn, were bound to the Itk SH3 domain. By examining the ability of different SH3 domains to interact with deletion variants of Sam 68 and WASP, we demonstrated that the Itk-SH3 domain and the SH3 domains of Src family kinases bind to overlapping but distinct sets of proline-rich regions in Sam 68 and WASP.

L5 ANSWER 62 OF 95 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 96279212 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8663178
TITLE: Rapid identification of phosphopeptide ligands for SH2 domains. Screening of **peptide libraries** by fluorescence-activated bead sorting.
AUTHOR: Muller K; Gombert F O; Manning U; Grossmuller F; Graff P; Zaegel H; Zuber J F; Freuler F; Tschopp C; Baumann G
CORPORATE SOURCE: Sandoz Pharma Ltd., Preclinical Research, CH-4002 Basel, Switzerland.
SOURCE: Journal of biological chemistry, (1996 Jul 12) 271 (28) 16500-5.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960911
Last Updated on STN: 19960911
Entered Medline: 19960829

AB A method for the identification of high-affinity ligands to SH2 domains by fluorescence-activated bead sorting (FABS) was established. Recombinant SH2 domains, expressed as glutathione S-transferase (GST) fusion proteins, were incubated with a phosphotyrosine (Y*)-containing **peptide library**. 6.4 x 10(5) individual peptides of nine amino acids in length (EPX6Y*X19X7X19X7X6) were each displayed on beads. Phosphopeptide interaction of a given SH2 domain was monitored by binding of fluorescein isothiocyanate-labeled antibodies directed against GST. High-fluorescence beads were isolated by flow cytometric sorting. Subsequent pool sequencing of the selected beads revealed a distinct pattern of phosphotyrosine-containing motifs for each individual SH2 domain: the SH2 domain of the adapter protein Grb2 predominantly selected beads with the sequence Y*ENDP, whereas the C-terminal SH2 domain of the **tyrosine kinase** Syk selected Y*EELD, each motif representing the most frequently found residues C-terminal to the phosphotyrosine. For deconvolution studies, soluble phosphopeptides comprising variations of the Grb2 motifs were resynthesized and analyzed by surface plasmon resonance.

L5 ANSWER 63 OF 95 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 96279132 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8663233
TITLE: Specificity of LIM domain interactions with receptor **tyrosine** kinases.
AUTHOR: Wu R; Durick K; Songyang Z; Cantley L C; Taylor S S; Gill G N
CORPORATE SOURCE: Department of Biology, University of California San Diego, La Jolla, California 92093-0650, USA.
CONTRACT NUMBER: DK 13149 (NIDDK)
T32CA 02523 (NCI)
SOURCE: Journal of biological chemistry, (1996 Jul 5) 271 (27) 15934-41.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960911
Last Updated on STN: 20000303
Entered Medline: 19960829

AB LIM domains, Cys-rich motifs containing approximately 50 amino acids found in a variety of proteins, are proposed to direct protein*protein interactions. To identify structural targets recognized by LIM domains, we have utilized random **peptide library** selection, the yeast two-hybrid system, and glutathione S-transferase fusions. Enigma contains three LIM domains within its carboxyl terminus and LIM3 of Enigma specifically recognizes active but not mutant endocytic codes of the insulin receptor (InsR) (Wu, R. Y., and Gill, G. N. (1994) J. Biol. Chemical 269, 25085-25090). Interaction of two random **peptide libraries** with glutathione S-transferase-LIM3 of Enigma indicated specific binding to Gly-Pro-Hyd-Gly-Pro-Hyd-Tyr-Ala corresponding to the major endocytic code of InsR. Peptide competition demonstrated that both Pro and Tyr residues were required for specific interaction of InsR with Enigma. In contrast to LIM3 of Enigma binding to InsR, LIM2 of Enigma associated specifically with the receptor **tyrosine kinase**, Ret. Ret was specific for LIM2 of Enigma and did not bind other LIM domains tested. Mutational analysis indicated that the residues responsible for binding to Enigma were localized to the carboxyl-terminal 61 amino acids of Ret. A peptide corresponding to the carboxyl-terminal 20 amino acids of Ret dissociated Enigma and Ret complexes, while a mutant that changed Asn-Lys-Leu-Tyr in the peptide to Ala-Lys-Leu-Ala or a peptide corresponding to exon16 of InsR failed to disrupt the complexes, indicating the Asn-Lys-Leu-Tyr sequence of Ret is essential to the recognition motif for LIM2 of Enigma. We conclude that LIM domains of Enigma recognize **tyrosine**-containing motifs with specificity residing in both the LIM domains and in the target structures.

L5 ANSWER 64 OF 95 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 96215053 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8621456
TITLE: The multiple endocrine neoplasia type 2B point mutation alters long-term regulation and enhances the transforming capacity of the epidermal growth factor receptor.
AUTHOR: Pandit S D; Donis-Keller H; Iwamoto T; Tomich J M; Pike L J
CORPORATE SOURCE: Washington University School of Medicine, Department of Surgery, St. Louis, Missouri 63110, USA.
SOURCE: Journal of biological chemistry, (1996 Mar 8) 271 (10) 5850-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960627
Last Updated on STN: 20000303
Entered Medline: 19960620

AB The RET proto-oncogene encodes a member of the receptor **tyrosine kinase** family. Multiple endocrine neoplasia type 2B (MEN 2B) is caused by the mutation of a conserved methionine to a threonine in the catalytic domain of the RET **kinase**. When the MEN 2B point mutation was introduced into the epidermal growth factor (EGF) receptor (M857T EGFR), the intrinsic **tyrosine kinase** activity of the mutant receptor was similar to that of wild-type EGF receptor and

remained ligand-dependent. However, the mutant receptor showed an enhanced transforming capacity compared to the wild-type receptor as judged by its ability to mediate the growth of NIH 3T3 cells in soft agar. Using the oriented **peptide library** approach to examine substrate specificity, the M857T mutation was found to be associated with a decrease in the selectivity of the receptor for Phe and an increase in the selectivity for acidic residues at the P + 1 position as compared to wild-type EGF receptor. Short-term responses to EGF were similar in cells expressing wild-type and M857T EGF receptors. However, significant differences in receptor down-regulation were observed between the two receptors. These data demonstrate that the MEN 2B point mutation alters the substrate specificity of receptor **tyrosine** kinases and suggest that the enhanced oncogenesis associated with the MEN 2B mutation may be due in part to alterations in receptor regulation.

L5 ANSWER 65 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:696101 CAPLUS
DOCUMENT NUMBER: 125:325849
TITLE: Mapping the specificity of an antibody against an oncogenic sequence using **peptide** combinatorial **libraries** and substitution analogs: Implications for breast cancer detection
AUTHOR(S): Appel, J. R.; Buencamino, J.; Houghten, R. A.; Pinilla, C.
CORPORATE SOURCE: Torrey Pines Institute Molecular Studies, San Diego, CA, 92121, USA
SOURCE: Peptides: Chemistry, Structure and Biology, Proceedings of the American Peptide Symposium, 14th, Columbus, Ohio, June 18-23, 1995 (1996), Meeting Date 1995, 794-795. Editor(s): Kaumaya, Pravin T. P.; Hodges, Robert S. Mayflower Scientific: Kingswinford, UK.
CODEN: 63NTAF
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Proteins encoded by oncogenes, such as c-erbB2, contain a consensus region that has homol. with growth factor receptors and protein kinases. These proteins are known to be implicated in breast cancer by their presence in clin. samples of cancer patients. The authors have been studying the specificities of a number of mAbs raised against this consensus region. Here, the authors characterized the specificity of a mAb raised against a synthetic peptide from this consensus region using individual substitution analogs and **peptide** combinatorial **libraries**.

L5 ANSWER 66 OF 95 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 96397639 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8804533
TITLE: Identification of GIYWHHY as a novel peptide substrate for human p60c-src protein **tyrosine kinase**.
AUTHOR: Lou Q; Leftwich M E; Lam K S
CORPORATE SOURCE: Arizona Cancer Center, Tucson, USA.
CONTRACT NUMBER: CA17094 (NCI)
CA23074 (NCI)
CA57733 (NCI)
SOURCE: Bioorganic & medicinal chemistry, (1996 May) 4 (5) 677-82. Journal code: 9413298. ISSN: 0968-0896.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961025

Last Updated on STN: 19961025
Entered Medline: 19961016

AB We have recently determined that -Ile-Tyr- were the two critical residues as a peptide substrate for p60c-src protein **tyrosine kinase** (Lou, Q. et al., Lett. Peptide Sci., 1995, 2, 289). Here, we report on the design and synthesis of a secondary 'one-bead, one-compound' combinatorial **peptide library** based on this dipeptide motif (XIYXXXX, where X = all 19 eukaryotic amino acids except for cysteine). This secondary library was screened for its ability to be phosphorylated by p60c-src PTK using [gamma 32P]ATP as a tracer. Five of the strongest [32P]-labeled peptide-beads were identified and microsequenced: GIYWHHY, KIYDDYE, EIYEENG, EIYEEYE, and YIYEEED. A solid-phase phosphorylation assay was used to evaluate the structure-activity relationship of GIYWHHY. It was determined that Ile2, Tyr3, His5, and His6 were crucial for its activity as a substrate.

L5 ANSWER 67 OF 95 MEDLINE on STN DUPLICATE 25
ACCESSION NUMBER: 96326700 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8709147
TITLE: Catalytic specificity of phosphotyrosine kinases Blk, Lyn, c-Src and Syk as assessed by phage display.
AUTHOR: Schmitz R; Baumann G; Gram H
CORPORATE SOURCE: Sandoz Pharma Ltd, Basel, Switzerland.
SOURCE: Journal of molecular biology, (1996 Aug 2) 260 (5) 664-77.
Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 20000303
Entered Medline: 19960912

AB Protein **tyrosine** kinases (PTKs) are implicated in cell proliferation, differentiation, and receptor-mediated signalling events. Recruitment of intracellular PTKs into the signalling complex, often localized at the inner surface of the cell membrane, involves SH2 and SH3 domains attached to the catalytic **kinase** domain. While the interaction of SH2 and SH3 domains with their target sequences is well documented in a number of cases, the contribution of the catalytic domain itself in conferring specificity to a given signal cascade is not fully understood. We addressed this question and employed the phage display technique to assess the substrate requirements for the highly related Src-like PTKs c-Src, Blk, Lyn and the distantly related Syk. A diverse **peptide library** on phage was established, and after multiple rounds of phosphorylation and selection of phage displaying phosphotyrosine-containing peptides, canonical substrate sequences for each of the PTKs were enriched. The PTKs Blk and Lyn implicated in B cell signalling were found to prefer peptide substrates of the structure I/L-Y-D/E-X-L which resemble critical features of the ITAM motifs found in, e.g. the intracellular components Ig-alpha and Ig-beta of the beta cell receptor. All Src-like PTKs had a requirement for isoleucine or leucine in the position -1 with respect to the phosphorylated **tyrosine** residue in position 0. While Blk and Lyn had a strong preference for a negatively charged amino acid in position +1, c-Src preferred tryptophan or glycine in this position. Syk, not belonging to the Src-like PTK family, revealed a distinct substrate requirement for aspartic acid in position -1 and glutamic acid in position +1. In general, all PTKs we have tested had a strong preference for a particular amino acid in the positions -1 and +1 adjacent to the **tyrosine** residue.

L5 ANSWER 68 OF 95 MEDLINE on STN DUPLICATE 26
ACCESSION NUMBER: 97026336 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8872515
TITLE: Substrate specificity and inhibitor profile of human recombinant p56lck from a baculovirus expression vector.
AUTHOR: Flotow H; Purton T J; Whitaker D P; Williams D H; Wilkinson S E
CORPORATE SOURCE: Roche Research Centre, Welwyn Garden City, Herts, UK.
SOURCE: Inflammation research : official journal of the European Histamine Research Society ... [et al.], (1996 Aug) 45 (8) 412-5.
Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970523
Last Updated on STN: 20000303
Entered Medline: 19970513

AB p56lck, a member of the src family of non-receptor protein receptor kinases, is required for normal signal transduction through the T cell receptor. Inappropriate T cell activation and proliferation has been identified as an early event in auto-immune disease-agents which control T cell activation through modulation of p56lck **kinase** activity could therefore be potential therapeutic agents for a range of pathological conditions. To identify p56lck inhibitors, we have established an assay system suitable for the high throughput screening of compound libraries. The assay uses enzyme purified from baculovirus infected SF9 cells, and a novel peptidic substrate identified by L. Cantley from a degenerate combinatorial **peptide library** . We have used this assay system to screen a number of different compounds as potential inhibitors of p56lck. In addition, peptides based on the substrate sequence were also tested to identify a sequence that could be used in the rational design of peptide inhibitors of p56lck.

L5 ANSWER 69 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 27
ACCESSION NUMBER: 1997:82283 BIOSIS
DOCUMENT NUMBER: PREV199799373996
TITLE: Development of a selective pseudosubstrate-based peptide inhibitor of pp60-c-src protein **tyrosine kinase**.
AUTHOR(S): Wu, Jinzi J.; Phan, Hoang; Salmon, Sydney E.; Lam, Kit S. [Reprint author]
CORPORATE SOURCE: Arizona Cancer Cent., Dep. Med., Coll. Med., Univ. Arizona, 1515 N. Campbell Avenue, Tucson, AZ 85724, USA
SOURCE: Letters in Peptide Science, (1996) Vol. 3, No. 5, pp. 309-316.
ISSN: 0929-5666.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 1997
Last Updated on STN: 2 Apr 1997

AB Using a combinatorial **peptide library** method, we identified YIYGSFK as an efficient and specific peptide substrate for pp60-c-src protein **tyrosine kinase** (PTK) (Lam et al., Int. J. Pept. Protein Res., 45 (1995) 587). Employing YIYGSFK as a template, we synthesized and evaluated a series of pseudosubstrate-based inhibitors for pp60-c-src. We found that the efficiency of a given inhibitor was highly dependent on the specific **tyrosine** analog used at the phosphorylation site of the substrate. One of these

pseudosubstrate inhibitors, YI(2'-Nal)GSFK, selectively inhibited the **kinase** activity of pp60-c-src, with a K-i of 24 mu-M. This peptide inhibitor exhibited selectivity for pp60-c-src as compared to other PTKs tested, such as c-Abl and Bcr-Abl. Our results suggest that selective inhibitors for a specific PTK can be developed when the structure of a specific and efficient small peptide substrate for this PTK can be used as a template for structure modification.

L5 ANSWER 70 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 28

ACCESSION NUMBER: 1996:483189 BIOSIS
DOCUMENT NUMBER: PREV199699198445
TITLE: Structure-activity relationship of a novel peptide substrate for p60-c-src protein **tyrosine kinase**.
AUTHOR(S): Lou, Qiang; Wu, Jinzi; Salmon, Sydney E.; Lam, Kit S. [Reprint author]
CORPORATE SOURCE: Arizona Cancer Cent., Dep. Med., Univ. Arizona, 1515 N. Campbell Avenue, Tucson, AZ 85724, USA
SOURCE: Letters in Peptide Science, (1996) Vol. 2, No. 5, pp. 289-296.
ISSN: 0929-5666.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Oct 1996
Last Updated on STN: 10 Dec 1996

AB We recently reported the identification of a peptide (YIYGSFK) as an efficient substrate for p60-c-src using a random combinatorial **peptide library** screening method. Over 70 analogues of YIYGSFK were designed and synthesized on beads and their phosphorylation on solid phase by p60-c-src was quantitated by the PhosphorImager. A hydrophobic L-amino acid in position 2 and a basic amino acid in position 7 proved crucial for activity as a substrate. In addition, the L-**tyrosine** residue at position 3 was critical as the phosphorylation site and was found to be stereospecific, as substitution with the D-enantiomer at this position rendered the peptide totally inactive.

L5 ANSWER 71 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:1005479 CAPLUS
DOCUMENT NUMBER: 124:176900
TITLE: Protein Structure-Based Design of Combinatorial **Libraries**: Discovery of Non-**Peptide** Binding Elements to Src SH3 Domain
AUTHOR(S): Combs, Andrew P.; Kapoor, Tarun M.; Feng, Sibo; Chen, James K.; Daude-Snow, Lygia F.; Schreiber, Stuart L.
CORPORATE SOURCE: Howard Hughes Medical Institute, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Journal of the American Chemical Society (1996), 118(1), 287-8
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An approach to the discovery of cell permeable ligands to protein receptors is reported. By examining the 3-dimensional structures of SH3-peptide complexes determined by multidimensional NMR, a solid phase, encoded combinatorial synthesis was rationally designed to deliver nonpeptide binding elements to the site of a key specificity-determining pocket in SH3 domains. Fifteen ligands to the SH3 domain from the protein **tyrosine kinase** Src were selected from a pool of >1,000,000 spatially separated mols. These were resynthesized and individually analyzed for their ability to bind to the Src SH3 domain.

They were shown to be among the highest affinity SH3 ligands known, and they are the first SH3 ligands to use nonpeptide binding elements. The strategy used in this study is expected to be applicable to the discovery of ligands to proteins in general in general.

L5 ANSWER 72 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:695882 CAPLUS
DOCUMENT NUMBER: 126:3618
TITLE: Identification and characterization of a novel peptide substrate for P60c-src protein **tyrosine kinase** using a one-bead one-**peptide** combinatorial **peptide library** method
AUTHOR(S): Lam, K. S.; Lou, Q.; Wu, J.; Salmon, S. E.; Phan, H.
CORPORATE SOURCE: Arizona Cancer Center, University Arizona, Tucson, AZ, 85724, USA
SOURCE: Peptides: Chemistry, Structure and Biology, Proceedings of the American Peptide Symposium, 14th, Columbus, Ohio, June 18-23, 1995 (1996), Meeting Date 1995, 287-289. Editor(s): Kaumaya, Pravin T. P.; Hodges, Robert S. Mayflower Scientific: Kingswinford, UK.
CODEN: 63NTAF
DOCUMENT TYPE: Conference
LANGUAGE: English
AB We have successfully applied a one-bead one-**peptide** combinatorial **peptide library** method for identification of linear **peptide** substrate motifs for cAMP-dependent protein **kinase** (a serine/threonine protein **kinase**) and for P60c-src protein **tyrosine kinase** (PTK). In this method, we first incubated the **peptide**-bead **library** with [γ-32P]ATP and the protein **kinase**. After incubation, the beads were washed thoroughly with high salt buffer followed by heating with 1.0 M HCl for 5 min to remove all the non-covalent [γ-32P]ATP binding and washed thoroughly again. The beads were then suspended in molten 1.5% (w/v) agarose and plated on a glass plate. The bead-containing gel was then air-dried to form a film and exposed to an X-ray film. Autoradiog. was then used to localize the [32P]-labeled beads. The beads corresponding to the autoradiog. spots were removed and suspended in molten agarose solution again for secondary plating. With this dilution, single [32P]-labeled beads could be isolated for microsequencing.

L5 ANSWER 73 OF 95 MEDLINE on STN DUPLICATE 29
ACCESSION NUMBER: 97138127 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8985153
TITLE: Tight-binding inhibitory sequences against pp60(c-src) identified using a random 15-amino-acid **peptide library**.
AUTHOR: Nishi T; Budde R J; McMurray J S; Obeyesekere N U; Safdar N; Levin V A; Saya H
CORPORATE SOURCE: Department of Neuro-Oncology, The University of Texas, M.D. Anderson Cancer Center, Houston 77030, USA.
SOURCE: FEBS letters, (1996 Dec 16) 399 (3) 237-40.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219

Entered Medline: 19970130

AB A bacteriophage **peptide library** containing a random 15-amino-acid insert was screened for identification of peptide sequence(s) that bind pp60(c-src). Sequencing the random insert from more than 100 virions indicated that more than 60% of the phage virions that bound to this enzyme contained a GXXG sequence motif in which X was frequently a hydrophobic residue. The GXXG sequence was often repeated as GXXGXXG. Two nonameric peptides were synthesized to determine whether or not the peptide inhibits pp60(c-src) **tyrosine kinase** activity and the importance of the glycine residues within this sequence. The peptide containing glycine had a Ki of 24 microM, whereas replacing the glycines with proline increased the Ki value to 3.1 mM.

L5 ANSWER 74 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1996:523319 BIOSIS
DOCUMENT NUMBER: PREV199699245675
TITLE: **Tyrosine** protein **kinase** assays.
AUTHOR(S): Boutin, Jean A.
CORPORATE SOURCE: Inst. Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France
SOURCE: Journal of Chromatography B Biomedical Applications, (1996) Vol. 684, No. 1-2, pp. 179-199.
CODEN: JCBADL. ISSN: 0378-4347.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Nov 1996
Last Updated on STN: 23 Nov 1996

AB Protein kinases form a large family of enzymes that play a major role in a number of live processes. The study of their action is important for the understanding of the transformation mechanisms and of the normal and pathological growth events. The quality of an enzyme assay is often the key point of an enzymatic study. It must be flexible and compatible with various experimental conditions, such as those for the purification process, the screening of inhibitors and the substrate specificity studies. As will be shown in the present review, two categories of substrates, peptidic and proteic, should be distinguished. The use of peptide substrates facilitates the determination of the recognition requirements of the enzyme and of the kinetic effects of even minute variations in their sequence. These linear peptide structures are assumed to mimic a complex interaction between the enzyme and a proteic substrate in which distant amino acids in the sequence are vicinal in the folded substrate. Less amenable to a systematic study, but probably more adequate to investigate the natural substrate of a given **kinase**, are the proteic substrates. Obviously the tools to measure protein **kinase** activities are not the same in these two cases. The main difficulty in assaying protein kinases is the use of labelled gamma-ATP, mostly at large excess concentration, since the final product of the reaction has to be separated from the non-reacted labelled ATP. In the case of peptide substrates, the difficulty is to separate them from ATP basing on differences of molecular mass. Despite the efforts of many investigators to rely upon differences in solubility, in charges or in "affinity", this separation, which is crucial for the assay, is still an unsolved experimental problem. Chromatographic, as well as electrophoretic assays appeared relatively late in this domain, and more work in assessing new methodologies might bring new breakthroughs in the next few years. Specific, simple and reliable **kinase** assays are still a major challenge. Their improvement will help to conduct specificity studies, to elucidate complex growth mechanisms in which they are involved and to discover more selective potent inhibitors.

L5 ANSWER 75 OF 95 MEDLINE on STN DUPLICATE 30
ACCESSION NUMBER: 97000004 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8843147
TITLE: Amino-terminal sequence determinants for substrate recognition by platelet-derived growth factor receptor **tyrosine kinase**.
AUTHOR: Chan P M; Keller P R; Connors R W; Leopold W R; Miller W T
CORPORATE SOURCE: Department of Physiology and Biophysics, School of Medicine, State University of New York at Stony Brook 11794, USA.
CONTRACT NUMBER: CA58530 (NCI)
SOURCE: FEBS letters, (1996 Sep 30) 394 (2) 121-5.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19961205

AB The specificity of protein kinases has been shown to be influenced by residues near the phosphoaccepting amino acid. To examine the determinants for platelet-derived growth factor receptor (PDGFR) **tyrosine kinase** specificity, a **peptide library** with three degenerate positions N-terminal to **tyrosine** was constructed. After reaction with PDGFR, the most abundant phosphopeptides were isolated by immunoaffinity chromatography on a column containing monoclonal anti-phosphotyrosine antibody. Further separation of bound phosphopeptides with reverse-phase HPLC led to the identification of three optimal substrates for PDGFR: Ala-Ala-Asn-Ile-Thr-Tyr-Ala-Ala-Arg-Arg-Gly, Ala-Ala-Asn-Arg-Thr-Tyr-Ala-Ala-Arg-Arg-Gly and Ala-Ala-Leu-Ile-Thr-Tyr-Ala-Ala-Arg-Arg-Gly, where underlined residues are in the degenerate positions of the **peptide library**. Kinetic analyses of the three individual peptides (synthesized separately) showed these peptides to be among the best reported substrates for PDGFR. Our results expand the range of amino acid residues that have been shown to serve as recognition elements for receptor **tyrosine** kinases.

L5 ANSWER 76 OF 95 MEDLINE on STN
ACCESSION NUMBER: 97381298 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9238630
TITLE: Exploring antibody polyspecificity using synthetic combinatorial libraries.
AUTHOR: Appel J R; Buencamino J; Houghten R A; Pinilla C
CORPORATE SOURCE: Torrey Pines Institute for Molecular Studies, San Diego, CA 92121, USA.
SOURCE: Molecular diversity, (1996 Oct) 2 (1-2) 29-34.
Journal code: 9516534. ISSN: 1381-1991.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970902
Last Updated on STN: 19970902
Entered Medline: 19970821

AB Extensive mapping studies for seven antigen-antibody interactions have been carried out using both individual analogs and **peptide libraries**. With competitive ELISA, these studies have revealed that monoclonal antibodies exhibit a broad range of specificities, from antibodies that recognize only conservative substitutions for 1-2

positions of the antigenic determinant, to antibodies that recognize sequences that are completely unrelated to the parent antigen with comparable affinities. Synthetic combinatorial **libraries**, containing millions of **peptide** sequences, permit a more systematic and rapid evaluation of the extent of multiple-binding specificities of monoclonal antibodies than individual analogs. The **peptide libraries** used here comprise mixtures of compounds having specifically defined positions and mixture positions. The same diversity of sequences in different formats, which differ by the numbers of positions singularly defined and different locations defined within the sequence, can be examined. Comparison of the screening results, selection criteria of the most active mixtures, and different approaches used for the deconvolution of active individual compounds are discussed. Synthetic combinatorial libraries greatly facilitate the understanding of antigen-antibody interactions at the amino acid level and will assist in the development of improved immunodiagnostics.

L5 ANSWER 77 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:30491 CAPLUS
DOCUMENT NUMBER: 126:71811
TITLE: The structural basis for specificity in protein-**tyrosine kinase** signaling
AUTHOR(S): Cantley, Lewis C.; Zhou, Songyang
CORPORATE SOURCE: Harvard Medical School, Beth Israel Hospital, Boston, MA, 02115, USA
SOURCE: NATO ASI Series, Series H: Cell Biology (1996), 99(Tumor Biology), 5-16
CODEN: NASBE4; ISSN: 1010-8793
PUBLISHER: Springer
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 19 refs., on the structural basis for how protein **tyrosine** kinases find their specific targets in the cell interior. The following topics were discussed: SH2 domains, a **peptide library** for studying SH2 domain specificity, the structural basis for SH2 domain specificity, and substrate specificities of the catalytic sites of protein **tyrosine** kinases.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 78 OF 95 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:818757 CAPLUS
DOCUMENT NUMBER: 123:221801
TITLE: Methods for determining the phosphorylation site and substrate specificity of protein kinases
INVENTOR(S): Cantley, Lewis C.; Songyang, Zhou
PATENT ASSIGNEE(S): Beth Israel Hospital, USA
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9518823	A2	19950713	WO 1995-US147	19950106
WO 9518823	A3	19950803		
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5532167	A	19960702	US 1994-178570	19940107
PRIORITY APPLN. INFO.:			US 1994-178570 A	19940107

AB The invention provides a method for determining an amino acid sequence motif for a phosphorylation site of a protein **kinase**. In the method of the invention, a protein **kinase** is contacted with an oriented degenerate **peptide library**, peptides within the **library** which are substrates for the **kinase** are converted to phosphopeptides and the phosphopeptides are separated from non-phosphorylated peptides. The isolated phosphopeptides are sequenced and an amino acid sequence motif for the phosphorylation site is determined based upon the relative abundance of different amino acids residues at each degenerate position. The invention also provides peptide substrates for protein **kinase** A, cell cycle control kinases (including cyclin B/p33cdc2 and cyclin A/p33CDK2), src family kinases (including pp60c-src and pp60v-src), EGF receptor, p92c-fps/fes, lck, c-abl, PDGF receptor, FGF receptor, insulin receptor, casein **kinase** II, NIMA **kinase**, phosphorylase **kinase**, Cam **kinase** II and Erk1 based upon amino acid sequence motifs for the phosphorylation sites of these kinases.

L5 ANSWER 79 OF 95 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96020160 EMBASE
DOCUMENT NUMBER: 1996020160
TITLE: The specificity of the transforming growth factor β receptor kinases determined by a spatially addressable **peptide library**.
AUTHOR: Luo K.; Zhou P.; Lodish H.F.
CORPORATE SOURCE: Nine Cambridge Center, Whitehead Inst. for Biomedical Res.,Cambridge, MA 02142, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1995) Vol. 92, No. 25, pp. 11761-11765.
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 960130
Last Updated on STN: 960130

AB Type I and II receptors for the transforming growth factor β (TGF-β) are transmembrane serine/threonine kinases that are essential for TGF-β signaling. However, little is known about their in vivo substrates or signal transduction pathways. To determine the substrate specificity of these kinases, we developed combinatorial **peptide libraries** synthesized on a hydrophilic matrix that is easily accessible to proteins in aqueous solutions. When we subjected these libraries to phosphorylation by the cAMP- dependent protein **kinase**, we obtained the optimal peptide sequence RRXS(I/L/V), in perfect agreement with the substrate sequence deduced from mutagenesis and crystal structure analyses. By using the same libraries, we showed that the optimal substrate peptide for both the type I and II TGF-β receptors was KKKKKK(S/T)XXX. Since the two kinases are thought to play different roles in intracellular signal transduction, it was a surprise to find that they have almost identical substrate specificity. Our method is direct, sensitive, and simple and provides information about the **kinase** specificity for all the amino acid residues at each position.

L5 ANSWER 80 OF 95 MEDLINE on STN DUPLICATE 31

ACCESSION NUMBER: 96028197 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7473555
TITLE: Identification of efficient pentapeptide substrates for the

tyrosine kinase pp60c-src.

AUTHOR: Nair S A; Kim M H; Warren S D; Choi S; Songyang Z; Cantley L C; Hangauer D G

CORPORATE SOURCE: Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo 14260-1200, USA.

CONTRACT NUMBER: R01 CA52800 (NCI)

SOURCE: Journal of medicinal chemistry, (1995 Oct 13) 38 (21) 4276-83.
Journal code: 9716531. ISSN: 0022-2623.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199511

ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 20030316
Entered Medline: 19951128

AB The development of inhibitors of protein **tyrosine** kinases (PTKs) is a promising approach to obtaining new therapeutic agents for a variety of diseases, particularly cancer. However, the discovery of peptide-based inhibitors has been hindered by the lack of small peptide substrate sequences (i.e. five residues or less) with which a variety of inhibitor designs could be readily evaluated by replacing the Tyr with natural and unnatural amino acids. These prototypical small peptide inhibitors could then form the basis for designing analogous conformationally constrained, peptide-mimetic or non-peptide inhibitors with improved therapeutic potential. In this study we have identified the best known small peptide substrate for the PTK pp60c-src, which is the parent of the src family of nonreceptor PTKs. This pentapeptide substrate, Ac-Ile-Tyr-Gly-Glu-Phe-NH2, has a Km of 368 microM and Vmax of 1.02 mumol/min/mg when tested utilizing the assay methodology of Budde et al. (Anal. Biochem. 1992, 200, 347-351) after a series of modifications were made to more closely simulate the conditions inside a typical mammalian cell. This substrate was designed from information obtained by Songyang et al. (Nature 1995, 373, 536-539) with a 2.5 billion member combinatorial **library** of **peptide** substrates for pp60c-src. A second pentapeptide substrate, Ac-Glu-Asp-Ala-Ile-Tyr-NH2, with a weaker binding affinity (Km = 880 microM) but improved Vmax (1.86 mumol/min/mg), was also identified. This peptide was designed from the pp60c-src autophosphorylation sequence and information obtained by Songyang et al. (Ibid.) and Till et al. (J. Biol. Chemical 1994, 269, 7423-7428) with combinatorial **libraries** of **peptide** substrates. These new substrates provide sufficient binding affinities and rates of phosphorylation to be utilized for evaluating the relative effectiveness of various reversible and mechanism-based irreversible inhibitor designs for pp60c-src while appended to easily prepared small peptides.

L5 ANSWER 81 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 32

ACCESSION NUMBER: 1995:217591 BIOSIS

DOCUMENT NUMBER: PREV199598231891

TITLE: Proline-rich sequences that bind to Src homology 3 domains with individual specificities.

AUTHOR(S): Alexandropoulous, Konstantina; Cheng, Genhong; Baltimore, David

CORPORATE SOURCE: Dep. Biol., Massachusetts Inst. Technol., 77 Massachusetts Ave., Cambridge, MA 02139, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1995) Vol. 92, No. 8, pp. 3110-3114.
CODEN: PNASA6. ISSN: 0027-8424.

DOCUMENT TYPE: Article

LANGUAGE: English
ENTRY DATE: Entered STN: 31 May 1995
Last Updated on STN: 1 Jun 1995

AB To study the binding specificity of Src homology 3 (SH3) domains, we have screened a mouse embryonic expression **library** for **peptide** fragments that interact with them. Several clones were identified that express fragments of proteins which, through proline-rich binding sites, exhibit differential binding specificity to various SH3 domains. Src-SH3-specific binding uses a sequence of 7 aa of the consensus RPLPXXP, in which the N-terminal arginine is very important. The SH3 domains of the Src-related kinases Fyn, Lyn, and Hck bind to this sequence with the same affinity as that of the Src SH3. In contrast, a quite different proline-rich sequence from the Btk protein **kinase** binds to the Fyn, Lyn, and Hck SH3 domains, but not to the Src SH3. Specific binding of the Abl SH3 requires a longer, more proline-rich sequence but no arginine. One clone that binds to both Src and Abl SH3 domains through a common site exhibits reversed binding orientation, in that an arginine indispensable for binding to all tested SH3 domains occurs at the C terminus. Another clone contains overlapping yet distinct Src and Abl SH3 binding sites. Binding to the SH3 domains is mediated by a common PXXP amino acid sequence motif present on all ligands, and specificity comes about from other interactions, often ones involving arginine. The rules governing in vivo usage of particular sites by particular SH3 domains are not clear, but one binding orientation may be more specific than another.

L5 ANSWER 82 OF 95 MEDLINE on STN DUPLICATE 33
ACCESSION NUMBER: 96031531 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7558590
TITLE: Identification and characterization of a novel synthetic peptide substrate specific for Src-family protein **tyrosine** kinases.
AUTHOR: Lam K S; Wu J; Lou Q
CORPORATE SOURCE: Arizona Cancer Center, University of Arizona, Tucson, USA.
CONTRACT NUMBER: CA13074 (NCI)
CA17094 (NCI)
CA57723 (NCI)
SOURCE: International journal of peptide and protein research, (1995 Jun) 45 (6) 587-92.
Journal code: 0330420. ISSN: 0367-8377.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951106

AB Using a random combinatorial **peptide library** method [Wu, J., Ma, Q. N. & Lam, K. S. (1994) Biochemistry 33, 14825-14833] a novel peptide, YIYGSFK, was identified as a substrate for p60c-src protein **tyrosine kinase**. Mass spectrometric analysis showed that **tyrosine**-3 from the N-terminus was the phosphorylation site. Kinetic studies showed that the Km of YIYGSFK for p60c-src was 55 microM, about 6.4-fold lower than a peptide derived from p34cdc2 [cdc2(6-20), KVEKIGEGTYGVVYK], which had been reported to be a specific and efficient substrate for the Src-family protein **tyrosine** kinases. Comparison of the specificity of YIYGSFK and cdc2(6-20) as a substrate for various Src-family and non-Src-family protein **tyrosine** kinases suggests that YIYGSFK is a much more specific and efficient substrate for the Src-family protein **tyrosine** kinases.

L5 ANSWER 83 OF 95 MEDLINE on STN DUPLICATE 34
ACCESSION NUMBER: 95147977 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7845468
TITLE: Catalytic specificity of protein-**tyrosine** kinases is critical for selective signalling.
COMMENT: Comment in: Nature. 1995 Feb 9;373(6514):477-8. PubMed ID: 7845456
AUTHOR: Songyang Z; Carraway K L 3rd; Eck M J; Harrison S C; Feldman R A; Mohammadi M; Schlessinger J; Hubbard S R; Smith D P; Eng C; +
CORPORATE SOURCE: Department of Medicine, Beth Israel Hospital, Boston, Massachusetts 02215.
SOURCE: Nature, (1995 Feb 9) 373 (6514) 536-9.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950316
Last Updated on STN: 20030316
Entered Medline: 19950303

AB How do distinct protein-**tyrosine** kinases activate specific down-stream events? Src-homology-2 (SH2) domains on **tyrosine** kinases or targets of **tyrosine** kinases recognize phosphotyrosine in a specific sequence context and thereby provide some specificity. The role of the catalytic site of **tyrosine** kinases in determining target specificity has not been fully investigated. Here we use a degenerate **peptide library** to show that each of nine **tyrosine** kinases investigated has a unique optimal peptide substrate. We find that the cytosolic **tyrosine** kinases preferentially phosphorylate peptides recognized by their own SH2 domains or closely related SH2 domains (group I; reference 3), whereas receptor **tyrosine** kinases preferentially phosphorylate peptides recognized by subsets of group III SH2 domains. The importance of these findings for human disease is underscored by our observation that a point mutation in the RET receptor-type **tyrosine kinase**, which causes multiple endocrine neoplasia type 2B, results in a shift in peptide substrate specificity.

L5 ANSWER 84 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:187226 BIOSIS
DOCUMENT NUMBER: PREV199598201526
TITLE: Identification and characterization of a novel peptide substrate specific for Src-family protein **tyrosine kinase** using a combinatorial **peptide library** method.
AUTHOR(S): Lam, K. S. [Reprint author]; Wu, J.; Lu, Q. [Reprint author]
CORPORATE SOURCE: Ariz. Cancer Cent., Tucson, AZ 85724, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1995) Vol. 36, No. 0, pp. 511.
Meeting Info.: Eighty-sixth Annual Meeting of the American Association for Cancer Research. Toronto, Ontario, Canada. March 18-22, 1995.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 May 1995
Last Updated on STN: 9 Jun 1995

L5 ANSWER 85 OF 95 MEDLINE on STN DUPLICATE 35
ACCESSION NUMBER: 96108162 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8578591
TITLE: Recognition and specificity in protein **tyrosine kinase**-mediated signalling.
AUTHOR: Songyang Z; Cantley L C
CORPORATE SOURCE: Division of Signal Transduction, Beth Israel Hospital, Boston, MA 02115, USA.
SOURCE: Trends in biochemical sciences, (1995 Nov) 20 (11) 470-5. Ref: 46
Journal code: 7610674. ISSN: 0968-0004.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960321
Last Updated on STN: 20030316
Entered Medline: 19960313

AB There are several factors that contribute to the specificities of protein **tyrosine** kinases (PTKs) in signal transduction pathways. While protein-protein interaction domains, such as the Src homology (SH2 and SH3) domains, regulate the cellular localization of PTKs and their substrates, the specificities of PTKs are ultimately determined by their catalytic domains. The use of **peptide libraries** has revealed the substrate specificities of SH2 domains and PTK catalytic domains, and has suggested cross-talk between these domains.

L5 ANSWER 86 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1996:453684 BIOSIS
DOCUMENT NUMBER: PREV199699176040
TITLE: Use of phage **peptide libraries** for studying the specificity of **tyrosine** phosphorylation and recognition.
AUTHOR(S): Dente, Luciana; Vetriani, Costantino; Cesareni, Gianni
CORPORATE SOURCE: Dep. Biol., "Tor Vergata", Rome, Italy
SOURCE: Physiological Chemistry and Physics and Medical NMR, (1995) Vol. 27, No. 4, pp. 260.
Meeting Info.: 1st International Symposium on Trends in Peptide Research. Perugia, Italy. May 14-18, 1995.
CODEN: PCPNER. ISSN: 0748-6642.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Oct 1996
Last Updated on STN: 7 Oct 1996

L5 ANSWER 87 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 36
ACCESSION NUMBER: 1995:551794 BIOSIS
DOCUMENT NUMBER: PREV199698566094
TITLE: Discovery, development, and testing of substrates and inhibitors of PP60-C-SRC.
AUTHOR(S): Budde, Raymond J. A. [Reprint author]; McMurray, John S. [Reprint author]; Saya, Hideyuki [Reprint author]; Gallick, Gary E.; Levin, Victor A. [Reprint author]
CORPORATE SOURCE: Dep. Neuro-Oncol., Univ. Tex., M.D. Anderson Cancer Cent., 1515 Holcombe Blvd., Houston, TX 77030, USA

SOURCE: International Journal of Pharmacognosy, (1995) Vol. 33, No. SUPPL., pp. 27-34.
CODEN: IJPYEW. ISSN: 0925-1618.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Dec 1995
Last Updated on STN: 31 Dec 1995

AB Currently, there are no specific protein **tyrosine kinase** inhibitors available. This review summarizes our efforts to develop an active-site-directed inhibitor of pp60-c-src. Initial efforts are directed at determining substrate specificity with synthetic peptides and at developing a biological system to test the potential of pp60-c-src inhibitors to effectively inhibit the growth of pp60-c-src activated cell lines. To meet these goals, we have developed new methods for purifying recombinant pp60-c-src, assaying **tyrosine kinase** activity, synthesizing cyclic peptides, and generating random **peptide libraries**. In addition, we discuss the generation of potential artifacts while using polyhydroxy aromatic compounds as **tyrosine kinase** inhibitors.

L5 ANSWER 88 OF 95 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1994-279762 [34] WPIDS
DOC. NO. CPI: C1994-127736
TITLE: Identifying anti-proliferative peptide(s) which specifically bind to immunoglobulin super-family species idiotype - especially to inhibit B-cell lymphoma and leukocytic leukaemia cell proliferation, for anti-idiotype therapy.
DERWENT CLASS: B04 D16
INVENTOR(S): BHATT, R R; DOWER, W J; LEVY, R; RENSCHLER, M F
PATENT ASSIGNEE(S): (AFFY-N) AFFYMAX TECHNOLOGIES NV; (STRD) UNIV LELAND STANFORD JUNIOR; (BHAT-I) BHATT R R; (DOWE-I) DOWER W J; (LEVY-I) LEVY R; (RENS-I) RENSCHLER M F
COUNTRY COUNT: 20
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9418345	A1	19940818	(199434)*	EN	69
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9461711	A	19940829	(199501)		
US 5512435	A	19960430	(199623)		31

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9418345	A1	WO 1994-US1319	19940204
AU 9461711	A	AU 1994-61711	19940204
		WO 1994-US1319	19940204
US 5512435	A	US 1993-14426	19930205

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9461711	A	Based on	WO 9418345

PRIORITY APPLN. INFO: US 1993-14426 19930205; US 1993-153341 19931115
AN 1994-279762 [34] WPIDS

AB WO 9418345 A UPAB: 19941013
Antiproliferative peptides are identified by (i) obtaining from a patient, a predetermined cell population comprising cells which express on their extracellular surface an immunoglobulin superfamily species (IgSS) having a single idiotype characteristic to the cell population; (ii) contacting under aqueous binding conditions the IgSS to a **peptide library** comprising members having distinct **peptide** sequences; (iii) identifying a **peptide library** member that specifically binds to the IgSS idiotype as an anti-idiotype peptide (A); (iv) contacting (A) to the predetermined cell population under growth conditions and measuring an indicator of cell proliferation or activation in the population; and (v) identifying an (A) which inhibits cell proliferation of the predetermined cell population as an antiproliferative peptide (A1). Opt. the aminoacid sequence of this (A1) is determined.

USE/ADVANTAGE - Non-immunoglobulin antiproliferative peptides which specifically bind to an IgSS idiotype present on lymphoma cells or lymphocytic leukaemia cells are useful for inhibiting the proliferation of such cells (claimed). Thus, a lymphoma or lymphocytic leukaemia can be treated using the peptides (claimed) which includes clonal energy, modulate **tyrosine kinase** activity and/or induce apoptosis in cultured cells of the individual B-cell lymphoma. The peptides can be used individually, as complexes of crosslinked peptides or can be conjugated to deliver toxins or radionuclides to neoplastic cells bearing the specific IgSS.

Dwg.0/6

ABEQ US 5512435 A UPAB: 19960610
A new method for identifying antiproliferative peptides, comprising the steps of:

i) obtaining a predetermined cell population from a patient, wherein said predetermined cell population comprises cells expressing on their extracellular surface an immunoglobulin superfamily species having a single idiotype characteristic to the predetermined cell population;

ii) contacting under aqueous binding conditions said immunoglobulin superfamily species to a **peptide library** comprising a multiplicity of **peptide library** members having distinct **peptide** sequences;

iii) identifying a **peptide library** member that binds specifically to said immunoglobulin superfamily species idiotype as an anti-idiotype peptide;

iv) contacting under growth conditions said anti-idiotype peptide to said predetermined cell population or their clonal progeny and measuring an indicator of cell proliferation or activation in the predetermined cell population; and

v) identifying an anti-idiotype peptide which inhibits cell proliferation of the predetermined cell population as an antiproliferative peptide.

Dwg.0/3

L5 ANSWER 89 OF 95 MEDLINE on STN DUPLICATE 37
ACCESSION NUMBER: 94171764 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8125961
TITLE: Use of synthetic **peptide libraries** and phosphopeptide-selective mass spectrometry to probe protein **kinase** substrate specificity.
AUTHOR: Till J H; Annan R S; Carr S A; Miller W T
CORPORATE SOURCE: Department of Physiology and Biophysics, School of Medicine, State University of New York, Stony Brook 11794.
SOURCE: Journal of biological chemistry, (1994 Mar 11) 269 (10) 7423-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940420
Last Updated on STN: 19940420
Entered Medline: 19940412

AB To search for peptides which serve as substrates for protein kinases, an approach based on **peptide libraries** has been developed. These **peptide libraries** are chemically synthesized by a modified "divide-couple-recombine" strategy. After reaction with the **kinase** of interest, the most highly phosphorylated substrate (selected from the library) is identified using on-line liquid chromatography-electrospray mass spectrometry (LC-ESMS). Negative ion LC-ESMS with stepped collision energy is used to identify phosphorylated peptides in the enzyme reactions. As predicted, the cAMP-dependent protein **kinase** is shown to preferentially phosphorylate Kemptide (Leu-Arg-Arg-Ala-Ser-Leu-Gly) in a library consisting of 19 variants of Kemptide substituted at position 2. Additional experiments have been carried out on the nonreceptor **tyrosine kinase** v-Abl using a **peptide library** based on the v-Src autophosphorylation site (Arg-Arg-Leu-Ile-Glu-Asp-Ala-Glu-Tyr-Ala-Ala-Arg-Gly). These results indicate that Ile is the optimal residue at the position N-terminal to **tyrosine**. Individual peptides containing the Glu-Asp-Ala-Ile-Tyr motif have Vmax/Km values 6-fold higher than the peptide based on the autophosphorylation site itself, confirming the results of the library experiments. This motif has been identified in several **tyrosine** kinases at a position in the sequence not previously reported to serve as a phosphorylation or autophosphorylation site.

L5 ANSWER 90 OF 95 MEDLINE on STN
ACCESSION NUMBER: 95080244 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7988556
TITLE: Identification of Src, Fyn, Lyn, PI3K and Abl SH3 domain ligands using phage display libraries.
AUTHOR: Rickles R J; Botfield M C; Weng Z; Taylor J A; Green O M; Brugge J S; Zoller M J
CORPORATE SOURCE: ARIAD Pharmaceuticals, Cambridge, MA 02139.
CONTRACT NUMBER: CA27951 (NCI)
SOURCE: EMBO journal, (1994 Dec 1) 13 (23) 5598-604.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950124
Last Updated on STN: 19980206
Entered Medline: 19950109

AB Many proteins involved in intracellular signal transduction contain a small, 50-60 amino acid domain, termed the Src homology 3 (SH3) domain. This domain appears to mediate critical protein-protein interactions that are involved in responses to extracellular signals. Previous studies have shown that the SH3 domains from several proteins recognize short, contiguous amino acid sequences that are rich in proline residues. While all SH3 recognition sequences identified to date share a conserved P-X-X-P motif, the sequence recognition specificity of individual SH3 domains is poorly understood. We have employed a novel modification of phage display involving biased **libraries** to identify **peptide** ligands of the Src, Fyn, Lyn, PI3K and Abl SH3 domains. With biased libraries, we probed SH3 recognition over a 12 amino acid window. The Src SH3 domain prefers the sequence XXXRPLPPLPXP, Fyn prefers XXXRPLPP(I/L)PXX, Lyn

prefers RXXRPLPPLPXP, PI3K prefers RXXRPLPPLPP while the Abl SH3 domain selects phage containing the sequence PPPYPPPP(I/V)PXX. We have also analysed the binding properties of Abl and Src SH3 ligands. We find that although the phage-displayed Abl and Src SH3 ligands are proline rich, they are distinct. In surface plasmon resonance binding assays, these SH3 domains displayed highly selective binding to their cognate ligands when the sequences were displayed on the surface of the phage or as synthetic peptides. The selection of these high affinity SH3 peptide ligands provides valuable information on the recognition motifs of SH3 domains, serve as new tools to interfere with the cellular functions of SH3 domain-mediated processes and form the basis for the design of SH3-specific inhibitors of disease pathways.

L5 ANSWER 91 OF 95 MEDLINE on STN DUPLICATE 38
ACCESSION NUMBER: 95063992 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7526465
TITLE: Two binding orientations for peptides to the Src SH3 domain: development of a general model for SH3-ligand interactions.
AUTHOR: Feng S; Chen J K; Yu H; Simon J A; Schreiber S L
CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Chemistry, Harvard University, Cambridge, MA 02138.
CONTRACT NUMBER: GM44993 (NIGMS)
SOURCE: Science, (1994 Nov 18) 266 (5188) 1241-7.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 20000303
Entered Medline: 19941213

AB Solution structures of two Src homology 3 (SH3) domain-ligand complexes have been determined by nuclear magnetic resonance. Each complex consists of the SH3 domain and a nine-residue proline-rich **peptide** selected from a large **library** of ligands prepared by combinatorial synthesis. The bound ligands adopt a left-handed polyproline type II (PPII) helix, although the amino to carboxyl directionalities of their helices are opposite. The peptide orientation is determined by a salt bridge formed by the terminal arginine residues of the ligands and the conserved aspartate-99 of the SH3 domain. Residues at positions 3, 4, 6, and 7 of both peptides also intercalate into the ligand-binding site; however, the respective proline and nonproline residues show exchanged binding positions in the two complexes. These structural results led to a model for the interactions of SH3 domains with proline-rich peptides that can be used to predict critical residues in complexes of unknown structure. The model was used to identify correctly both the binding orientation and the contact and noncontact residues of a peptide derived from the nucleotide exchange factor Sos in association with the amino-terminal SH3 domain of the adaptor protein Grb2.

L5 ANSWER 92 OF 95 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1994:333720 BIOSIS
DOCUMENT NUMBER: PREV199497346720
TITLE: The use of **peptide libraries** to determine protein signaling pathways.
AUTHOR(S): Cantley, Lewis C. [Reprint author]; Songyang, Zhou
CORPORATE SOURCE: Dep. Cell Biol., Harvard Med. Sch., Boston, MA 02115, USA
SOURCE: FASEB Journal, (1994) Vol. 8, No. 7, pp. A1238.
Meeting Info.: 85th Annual Meeting of the American Society

for Biochemistry and Molecular Biology. Washington, D.C., USA. May 21-25, 1994.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 1994
Last Updated on STN: 3 Aug 1994

L5 ANSWER 93 OF 95 MEDLINE on STN
ACCESSION NUMBER: 97137730 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8983067
TITLE: Cell adhesion and tumor metastasis.
AUTHOR: Ruoslahti E
CORPORATE SOURCE: Cancer Research Center, La Jolla Cancer Research Foundation, CA 92037, USA.
SOURCE: Princess Takamatsu symposia, (1994) 24 99-105. Ref: 36
Journal code: 9301172.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970609
Last Updated on STN: 19970609
Entered Medline: 19970529

AB Integrins, among the various classes of cell adhesion receptors, are particularly associated with cell adhesion to extracellular matrices. They are heterodimeric transmembrane proteins with large ectodomains and short cytoplasmic tails. In many cases the sequence recognized by the integrins in the extracellular matrix proteins is the tripeptide Arg-Gly-Asp (RGD). Short synthetic peptides containing this sequence can inhibit tumor cell invasion in vitro and tumor dissemination in vivo. Because the alpha 5 beta 1 integrin appears to be the target of the peptides in many types of tumors, we have used phage display libraries to analyze the specificity of alpha 5 beta 1 and have isolated potent and specific inhibitors for this integrin. Increased expression of the alpha 5 beta 1 integrin, which is a fibronectin receptor, can also suppress cell migration and tumor cell invasion. We suggest this effect may be mediated through increased deposition of fibronectin matrix around the cells, because we found that the fibrillar matrix fibronectin suppresses tumor cell migration. There is increasing evidence that signals are elicited by the binding of integrins to their target proteins. This possibility has generated a great deal of interest in the cytoplasmic molecules that might mediate the integrin-associated signaling. At least two kinases, a novel **tyrosine kinase**, focal adhesion **kinase** (fak), and protein **kinase** C (PKC), are activated by integrin-mediated cell attachment. Moreover, a phosphorylated 190 kDa protein-associated with the alpha v beta 3 integrin has been found Anchorage dependence of cells and the migration-promoting activity of cell adhesion molecules are likely to depend on signal transduction through such molecules.

L5 ANSWER 94 OF 95 MEDLINE on STN DUPLICATE 39
ACCESSION NUMBER: 93126336 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8380494
TITLE: Molecular structure of a protein-**tyrosine** /threonine **kinase** activating p42 mitogen-activated protein (MAP) **kinase**: MAP **kinase kinase**.
AUTHOR: Wu J; Harrison J K; Vincent L A; Haystead C; Haystead T A;

Michel H; Hunt D F; Lynch K R; Sturgill T W
CORPORATE SOURCE: Department of Internal Medicine, University of Virginia, Charlottesville 22908.
CONTRACT NUMBER: DK41077 (NIDDK)
GM37537 (NIGMS)
HL08223 (NHLBI)
+
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1993 Jan 1) 90 (1) 173-7.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L04485
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930226
Last Updated on STN: 20000303
Entered Medline: 19930208

AB MAP kinases p42mapk and p44mapk participate in a protein **kinase** cascade(s) important for signaling in many cell types and contexts. Both MAP kinases are activated in vitro by MAP **kinase kinase** , a protein-**tyrosine** and threonine **kinase**. A MAP **kinase kinase** cDNA was isolated from a rat kidney **library** by using **peptide** sequence data we obtained from MAP **kinase kinase** isolated from rabbit skeletal muscle. The deduced sequence, containing 393 amino acids (predicted mass, 43.5 kDa), is most similar to byr1 (Bypass of ras1), a yeast protein **kinase** functioning in the mating pathway induced by pheromones in Schizosaccharomyces pombe. An unusually large insert is present in MAP **kinase kinase** between domains IX and X and may contribute to protein-protein interactions with MAP **kinase**. Major (2.7 kilobases) and minor (1.7 kilobases) transcripts are widely expressed in rat tissues and appear to be derived from a single gene.

L5 ANSWER 95 OF 95 MEDLINE on STN
ACCESSION NUMBER: 90221582 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2139203
TITLE: Direct cloning of leucine zipper proteins: Jun binds cooperatively to the CRE with CRE-BP1.
AUTHOR: Macgregor P F; Abate C; Curran T
CORPORATE SOURCE: Department of Molecular Oncology & Virology, Roche Institute of Molecular Biology, Nutley, New Jersey 07110.
SOURCE: Oncogene, (1990 Apr) 5 (4) 451-8.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900622
Last Updated on STN: 19900622
Entered Medline: 19900518

AB The proto-oncogene products Fos and Jun form a stable heterodimeric complex that functions in transcriptional regulation by interacting with the DNA sequence known as the AP-1 site. Dimer formation occurs through the leucine zipper, a structural motif involving a heptad repeat of leucine residues that is conserved in several fos- and jun-related genes. We have employed a novel cloning strategy to isolate genes encoding proteins capable of forming complexes with Jun. The procedure involves direct screening of a lambda gt11 cDNA **library** with a biotinylated Jun **polypeptide**. One clone isolated in this manner

encodes CRE-BP1, a leucine zipper-containing protein that binds to the cyclic AMP response element (CRE) as a homodimer. CRE-BP1 also forms heterodimers with Jun but not with Fos. Jun binds cooperatively to the CRE in association with CRE-BP1. Thus, the DNA-binding specificity and affinity of Jun are modulated by association with Fos or with CRE-BP1.

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=> e songyang zhou?/au
E1          119     SONGYANG Z/AU
E2          118     SONGYANG ZHOU/AU
E3            0 --> SONGYANG ZHOU?/AU
E4            1     SONGYANTAO/AU
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E6            1     SONGYING CHEN/AU
E7            1     SONGYU/AU
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=> e1 or 32
L6      1307952 "SONGYANG Z"/AU OR 32

=> e1 or e2
L7          237 "SONGYANG Z"/AU OR "SONGYANG ZHOU"/AU

=> (library or libraries) and l7
L8          139 (LIBRARY OR LIBRARIES) AND L7

=> (peptide or polypeptide) and l8
L9          102 (PEPTIDE OR POLYPEPTIDE) AND L8

=> kinase and l9
L10          66 KINASE AND L9

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          29 DUP REM L10 (37 DUPLICATES REMOVED)

=> d his

     (FILE 'HOME' ENTERED AT 17:51:21 ON 08 JUL 2005)

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, WPIDS' ENTERED AT 17:51:40 ON 08
     JUL 2005
L1         14659 (LIBRARY OR LIBRARIES) (5A) (PEPTIDE OR POLYPEPTIDE)
L2           394 TYROSINE AND KINASE AND L1
L3           209 PY>2000 AND L2
L4           185 L2 NOT L3
L5            95 DUP REM L4 (90 DUPLICATES REMOVED)
                 E SONGYANG ZHOU?/AU
L6        1307952 E1 OR 32
L7            237 E1 OR E2
L8            139 (LIBRARY OR LIBRARIES) AND L7
L9            102 (PEPTIDE OR POLYPEPTIDE) AND L8
L10            66 KINASE AND L9
L11            29 DUP REM L10 (37 DUPLICATES REMOVED)

=> l11 not l5
L12            18 L11 NOT L5
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=> t ti l12 1-18

L12 ANSWER 1 OF 18 MEDLINE on STN
TI Phosphopeptide binding specificities of BRCA1 COOH-terminal (BRCT) domains.

L12 ANSWER 2 OF 18 MEDLINE on STN
TI Domain-dependent function of the rasGAP-binding protein p62Dok in cell signaling.

L12 ANSWER 3 OF 18 MEDLINE on STN
TI **Peptide library** screening for determination of SH2 or phosphotyrosine-binding domain sequences.

L12 ANSWER 4 OF 18 MEDLINE on STN
TI Analysis of protein **kinase** specificity by **peptide libraries** and prediction of in vivo substrates.

L12 ANSWER 5 OF 18 MEDLINE on STN
TI The use of **peptide library** for the determination of **kinase peptide** substrates.

L12 ANSWER 6 OF 18 MEDLINE on STN
TI Determination of the specific substrate sequence motifs of protein **kinase** C isozymes.

L12 ANSWER 7 OF 18 MEDLINE on STN
TI A structural basis for substrate specificities of protein Ser/Thr kinases: primary sequence preference of casein kinases I and II, NIMA, phosphorylase **kinase**, calmodulin-dependent **kinase** II, CDK5, and Erk1.

L12 ANSWER 8 OF 18 MEDLINE on STN
TI Use of an oriented **peptide library** to determine the optimal substrates of protein kinases.

L12 ANSWER 9 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI **Peptide library** screening for determination of SH2 or phosphotyrosine-binding domain sequences.

L12 ANSWER 10 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Analysis of protein **kinase** specificity by **peptide libraries** and prediction of in vivo substrates.

L12 ANSWER 11 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Substrate specificity of a protein kinases.

L12 ANSWER 12 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Use of **peptide libraries** to define protein binding specificity.

L12 ANSWER 13 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI The use of **peptide library** for the determination of **kinase peptide** substrates.

L12 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Analysis of protein **kinase** specificity using oriented **peptide libraries**

L12 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Cyclic **peptide libraries** and methods of use thereof to identify binding motifs

L12 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Specific motifs recognized by the SH2 domains of Csk, 3BP2, fps/fes, GRB-2, HCP, SHC, Syk, and Vav

L12 ANSWER 17 OF 18 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI An Oriented **Peptide** Array **Library** (OPAL) Strategy to Study Protem-Protein Interactions.

L12 ANSWER 18 OF 18 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI Determining amino acid binding motifs for **kinase** phosphorylation sites is used to find **kinase** inhibitors useful to treat **kinase**-associated disease such as cancer, inflammatory diseases autoimmune disease and transplant rejection.

=> d ibib abs l12 1-18

L12 ANSWER 1 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2003605766 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14578343
TITLE: Phosphopeptide binding specificities of BRCA1 COOH-terminal (BRCT) domains.
AUTHOR: Rodriguez Maria; Yu Xiaochun; Chen Junjie; **Songyang Zhou**
CORPORATE SOURCE: Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: GM569209 (NIGMS)
SOURCE: Journal of biological chemistry, (2003 Dec 26) 278 (52) 52914-8. Electronic Publication: 2003-10-24.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20031223
Last Updated on STN: 20040211
Entered Medline: 20040210

AB Protein phosphorylation by protein kinases may generate docking sites for other proteins. It thus allows the assembly of signaling complexes in response to **kinase** activation. Several protein domains that bind phosphoserine or phosphothreonine residues have been identified, including the 14-3-3, PIN1, FHA, KIX, WD-40 domain, and polo box (Yaffe, M. B., and Elia, A. E. (2001) Curr. Opin. Cell Biol. 13, 131-138; Elia, A. E., Cantley, L. C., and Yaffe, M. B. (2003) Science 299, 1228-1231). The BRCA1 COOH-terminal (BRCT) domains are protein modules found in many proteins that regulate DNA damage responses (Koonin, E. V., Altschul, S. F., and Bork, P. (1996) Nat. Genet. 13, 266-268). Whether BRCT domains can mediate phosphorylation-dependent interactions has not been systematically investigated. We report here that the BRCT domains also recognize phosphopeptides. Oriented **peptide library** analysis indicated that the BRCT domains from BRCA1, MDC1, BARD1, and DNA Ligase IV preferred distinct phosphoserine-containing peptides. In addition, the interaction between BRCA1 and the BRCT binding motif of BACH1 was required for BACH1 checkpoint activity. Furthermore,

BRCT domains of the yeast DNA repair protein Rad9 could bind phosphopeptides, suggesting that the BRCT domains represent a class of ancient phosphopeptide-binding modules. Potential targets of BRCT domains were identified through data base search. Structural analysis of BRCA1 BRCT repeats also predicted conserved residues that may form the phosphopeptide-binding pocket. Thus, the BRCT repeats are a new family of phosphopeptide-binding domains in DNA damage responses.

L12 ANSWER 2 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2001286605 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11042170
TITLE: Domain-dependent function of the rasGAP-binding protein p62Dok in cell signaling.
AUTHOR: **Songyang Z**; Yamanashi Y; Liu D; Baltimore D
CORPORATE SOURCE: Verna and Marrs Mclean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, Texas 77030, USA.. songyang@bcm.tmc.edu
SOURCE: Journal of biological chemistry, (2001 Jan 26) 276 (4) 2459-65. Electronic Publication: 2000-10-19.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20030105
Entered Medline: 20010621

AB p62Dok, the rasGAP-binding protein, is a common target of protein-tyrosine kinases. It is one of the major tyrosine-phosphorylated molecules in v-Src-transformed cells. Dok consists of an amino-terminal Pleckstrin homology domain, a putative phosphotyrosine binding domain, and a carboxyl-terminal tail containing multiple tyrosine phosphorylation sites. The importance and function of these sequences in Dok signaling remain largely unknown. We have demonstrated here that the expression of Dok can inhibit cellular transformation by the Src tyrosine **kinase**. Both the phosphotyrosine binding domain and the carboxyl-terminal tail of Dok (in particular residues 336-363) are necessary for such activity. Using a combinatorial **peptide library** approach, we have shown that the Dok phosphotyrosine binding domain binds phosphopeptides with the consensus motif of Y/MXXNXL-phosphotyrosine. Furthermore, Dok can homodimerize through its phosphotyrosine binding domain and Tyr(146) at the amino-terminal region. Mutations of this domain or Tyr(146) that block homodimerization significantly reduce the ability of Dok to inhibit Src transformation. Our results suggest that Dok oligomerization through its multiple domains plays a critical role in Dok signaling in response to tyrosine **kinase** activation.

L12 ANSWER 3 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2001248290 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11305095
TITLE: **Peptide library** screening for determination of SH2 or phosphotyrosine-binding domain sequences.
AUTHOR: **Songyang Z**; Liu D
CORPORATE SOURCE: Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
SOURCE: Methods in enzymology, (2001) 332 183-95.
Journal code: 0212271. ISSN: 0076-6879.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20030316
Entered Medline: 20010510

L12 ANSWER 4 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2001248289 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11305094
TITLE: Analysis of protein **kinase** specificity by **peptide libraries** and prediction of in vivo substrates.
AUTHOR: **Songyang Z**
CORPORATE SOURCE: Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
SOURCE: Methods in enzymology, (2001) 332 171-83.
Journal code: 0212271. ISSN: 0076-6879.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

L12 ANSWER 5 OF 18 MEDLINE on STN
ACCESSION NUMBER: 1998183864 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9523263
TITLE: The use of **peptide library** for the determination of **kinase peptide** substrates.
AUTHOR: **Songyang Z**; Cantley L C
CORPORATE SOURCE: Harvard Medical School, Beth Israel Hospital, Boston, MA, USA.
SOURCE: Methods in molecular biology (Clifton, N.J.), (1998) 87 87-98.
Journal code: 9214969. ISSN: 1064-3745.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980430
Last Updated on STN: 19980430
Entered Medline: 19980422

L12 ANSWER 6 OF 18 MEDLINE on STN
ACCESSION NUMBER: 97150851 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8995387
TITLE: Determination of the specific substrate sequence motifs of protein **kinase** C isozymes.
AUTHOR: Nishikawa K; Toker A; Johannes F J; **Songyang Z**; Cantley L C
CORPORATE SOURCE: Division of Signal Transduction, Beth Israel Hospital, Boston, Massachusetts 02115, USA..
knishika@mercury.bih.harvard.edu
SOURCE: Journal of biological chemistry, (1997 Jan 10) 272 (2) 952-60.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19990129
Entered Medline: 19970212

AB Protein **kinase** C (PKC) family members play significant roles in a variety of intracellular signal transduction processes, but information about the substrate specificities of each PKC family member is quite limited. In this study, we have determined the optimal **peptide** substrate sequence for each of nine human PKC isozymes (alpha, betaI, betaII, gamma, delta, epsilon, eta, mu, and zeta) by using an oriented **peptide library**. All PKC isozymes preferentially phosphorylated peptides with hydrophobic amino acids at position +1 carboxyl-terminal of the phosphorylated Ser and basic residues at position -3. All isozymes, except PKC mu, selected peptides with basic amino acids at positions -6, -4, and -2. PKC alpha, -betaI, -betaII, -gamma, and -eta selected peptides with basic amino acid at positions +2, +3, and +4, but PKC delta, -epsilon, -zeta, and -mu preferred peptides with hydrophobic amino acid at these positions. At position -5, the selectivity was quite different among the various isozymes; PKC alpha, -gamma, and -delta selected peptides with Arg at this position while other PKC isozymes selected hydrophobic amino acids such as Phe, Leu, or Val. Interestingly, PKC mu showed extreme selectivity for peptides with Leu at this position. The predicted optimal sequences from position -3 to +2 for PKC alpha, -betaI, -betaII, -gamma, -delta, and -eta were very similar to the endogenous pseudosubstrate sequences of these PKC isozymes, indicating that these core regions may be important to the binding of corresponding substrate peptides. Synthetic peptides based on the predicted optimal sequences for PKC alpha, -betaI,-delta, -zeta, and -mu were prepared and used for the determination of Km and Vmax for these isozymes. As judged by Vmax/Km values, these peptides were in general better substrates of the corresponding isozymes than those of the other PKC isozymes, supporting the idea that individual PKC isozymes have distinct optimal substrates. The structural basis for the selectivity of PKC isozymes is discussed based on residues predicted to form the catalytic cleft.

L12 ANSWER 7 OF 18 MEDLINE on STN
ACCESSION NUMBER: 97042477 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8887677
TITLE: A structural basis for substrate specificities of protein Ser/Thr kinases: primary sequence preference of casein kinases I and II, NIMA, phosphorylase **kinase**, calmodulin-dependent **kinase** II, CDK5, and Erk1.
AUTHOR: **Songyang Z**; Lu K P; Kwon Y T; Tsai L H; Filhol O; Cochet C; Brickey D A; Soderling T R; Bartleson C; Graves D J; DeMaggio A J; Hoekstra M F; Blenis J; Hunter T; Cantley L C
CORPORATE SOURCE: Division of Signal Transduction, Beth Israel Hospital, Boston, Massachusetts 02215, USA.
SOURCE: Molecular and cellular biology, (1996 Nov) 16 (11) 6486-93. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20020420
Entered Medline: 19961216

AB We have developed a method to study the primary sequence specificities of protein kinases by using an oriented degenerate **peptide library**. We report here the substrate specificities of eight protein Ser/Thr kinases. All of the kinases studied selected distinct optimal substrates. The identified substrate specificities of these kinases, together with known crystal structures of protein **kinase** A, CDK2, Erk2, twitchin, and casein **kinase** I, provide a structural basis for the substrate recognition of protein Ser/Thr kinases. In particular, the specific selection of amino acids at the +1 and -3 positions to the substrate serine/threonine can be rationalized on the basis of sequences of protein kinases. The identification of optimal **peptide** substrates of CDK5, casein kinases I and II, NIMA, calmodulin-dependent kinases, Erk1, and phosphorylase **kinase** makes it possible to predict the potential in vivo targets of these kinases.

L12 ANSWER 8 OF 18 MEDLINE on STN
ACCESSION NUMBER: 95179522 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7874496
TITLE: Use of an oriented **peptide library** to determine the optimal substrates of protein kinases.
AUTHOR: **Songyang Z**; Blechner S; Hoagland N; Hoekstra M F; Piwnica-Worms H; Cantley L C
CORPORATE SOURCE: Division of Signal Transduction, Beth Israel Hospital, Boston, Massachusetts 02215.
SOURCE: Current biology : CB, (1994 Nov 1) 4 (11) 973-82. Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950419
Last Updated on STN: 20030204
Entered Medline: 19950331

AB BACKGROUND: Phosphorylation by protein kinases is an important general mechanism for controlling intracellular processes, and plays an essential part in the signal transduction pathways that regulate cell growth in response to extracellular signals. A great number of protein kinases have been discovered, and the identification of their biological targets is still a very active research area. Protein kinases must have the appropriate substrate specificity to ensure that signals are transmitted correctly. Previous studies have demonstrated the importance of primary sequences within substrate proteins in determining protein **kinase** specificity, but efficient ways of identifying these sequences are lacking. RESULTS: We have developed a new technique for determining the substrate specificity of protein kinases, using an oriented **library** of more than 2.5 billion **peptide** substrates. In this approach, the consensus sequence of optimal substrates is determined by sequencing the mixture of products generated during a brief reaction with the **kinase** of interest. The optimal substrate predicted for cAMP-dependent protein **kinase** (PKA) by this technique is consistent with the sequences of known PKA substrates. The optimal sequences predicted for cyclin-dependent kinases (CDKs) cyclin B-Cdc2 and cyclin A-CDK2 also agree well with sites thought to be phosphorylated in vivo by these kinases. In addition, we determined the optimal substrate for SLK1, a homologue of the STE20 protein serine **kinase** of hitherto unknown substrate specificity. We also discuss a model incorporating the optimal cyclin B-Cdc2 substrate into the known crystal structure of this **kinase**. CONCLUSIONS: Using the new technique we have developed, the sequence specificity of protein kinases can rapidly be predicted and, from this information, potential targets of the kinases

can be identified.

L12 ANSWER 9 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:482233 BIOSIS
DOCUMENT NUMBER: PREV200100482233
TITLE: **Peptide library** screening for determination of SH2 or phosphotyrosine-binding domain sequences.
AUTHOR(S): **Songyang, Zhou** [Reprint author]; Liu, Dan
CORPORATE SOURCE: Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Balch, W. E.; Der, Channing J.; Hall, Alan. Methods Enzymol., (2001) pp. 183-195. Methods in Enzymology. Regulators and effectors of small GTPases: Part F: Ras family I. print.
Publisher: Academic Press Inc., 525 B Street, Suite 1900, San Diego, CA, 92101-4495, USA; Academic Press Ltd., Harcourt Place, 32 Jamestown Road, London, NW1 7BY, UK.
Series: Methods in Enzymology.
CODEN: MENZAU. ISSN: 0076-6879. ISBN: 0-12-182233-8 (cloth).
DOCUMENT TYPE: Book
Book; (Book Chapter)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Oct 2001
Last Updated on STN: 23 Feb 2002

L12 ANSWER 10 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:482232 BIOSIS
DOCUMENT NUMBER: PREV200100482232
TITLE: Analysis of protein **kinase** specificity by **peptide libraries** and prediction of in vivo substrates.
AUTHOR(S): **Songyang, Zhou** [Reprint author]
CORPORATE SOURCE: Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Balch, W. E.; Der, Channing J.; Hall, Alan. Methods Enzymol., (2001) pp. 171-183. Methods in Enzymology. Regulators and effectors of small GTPases: Part F: Ras family I. print.
Publisher: Academic Press Inc., 525 B Street, Suite 1900, San Diego, CA, 92101-4495, USA; Academic Press Ltd., Harcourt Place, 32 Jamestown Road, London, NW1 7BY, UK.
Series: Methods in Enzymology.
CODEN: MENZAU. ISSN: 0076-6879. ISBN: 0-12-182233-8 (cloth).
DOCUMENT TYPE: Book
Book; (Book Chapter)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Oct 2001
Last Updated on STN: 23 Feb 2002

L12 ANSWER 11 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:278567 BIOSIS
DOCUMENT NUMBER: PREV200000278567
TITLE: Substrate specificity of a protein kinases.
AUTHOR(S): Cantley, Lewis C. [Inventor, Reprint author]; **Songyang, Zhou** [Inventor]

CORPORATE SOURCE: Cambridge, MA, USA
ASSIGNEE: Beth Israel Hospital, Boston, MA, USA
PATENT INFORMATION: US 6004757 19991221
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 21, 1999) Vol. 1229, No. 3. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jul 2000
Last Updated on STN: 7 Jan 2002

AB The invention provides a method for determining an amino acid sequence motif for a phosphorylation site of a protein **kinase**. In the method of the invention, a protein **kinase** is contacted with an oriented degenerate **peptide library**, peptides within the **library** which are substrates for the **kinase** are converted to phosphopeptides and the phosphopeptides are separated from non-phosphorylated peptides. The isolated phosphopeptides are sequenced and an amino acid sequence motif for the phosphorylation site is determined based upon the relative abundance of different amino acids residues at each degenerate position. The invention also provides **peptide** substrates for protein **kinase** A, cell cycle control kinases (including cyclin B/p33cdc2 and cyclin A/p33CDK2), src family kinases (including pp60c-src and pp60v-src), EGF receptor, p92c-fps/fes, lck, c-abl, PDGF receptor, FGF receptor, insulin receptor, casein **kinase** II, NIMA **kinase**, phosphorylase **kinase**, Cam **kinase** II and Erk1 based upon amino acid sequence motifs for the phosphorylation sites of these kinases.

L12 ANSWER 12 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:330969 BIOSIS
DOCUMENT NUMBER: PREV199800330969
TITLE: Use of **peptide libraries** to define protein binding specificity.
AUTHOR(S): Cantley, Lewis [Reprint author]; Yaffe, Michael; Nishikawa, Kiyotaka; **Songyang, Zhou**
CORPORATE SOURCE: Div. Signal Transduction, Beth Israel Hosp., Harvard Med. Sch., Boston, MA, USA
SOURCE: FASEB Journal, (April 24, 1998) Vol. 12, No. 8, pp. A1324. print.
Meeting Info.: Meeting of the American Society for Biochemistry and Molecular Biology. Washington, D.C., USA. May 16-20, 1998. American Society for Biochemistry and Molecular Biology.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1998
Last Updated on STN: 12 Aug 1998

L12 ANSWER 13 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:144591 BIOSIS
DOCUMENT NUMBER: PREV199800144591
TITLE: The use of **peptide library** for the determination of **kinase peptide** substrates.
AUTHOR(S): **Songyang, Zhou** [Reprint author]; Cantley, Lewis C.
CORPORATE SOURCE: Harvard Med. Sch., Beth Israel Hosp., Boston, MA, USA
SOURCE: Cabilly, S. [Editor]. METH MOL BIOL, (1998) pp. 87-98.

Methods in Molecular Biology; Combinatorial peptide library protocols. print.
Publisher: Humana Press Inc., Suite 808, 999 Riverview Drive, Totowa, New Jersey 07512, USA. Series: Methods in Molecular Biology.
CODEN: MMBYBO. ISSN: 0097-0816. ISBN: 0-89603-392-9.

DOCUMENT TYPE: Book
Book; (Book Chapter)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Mar 1998
Last Updated on STN: 31 Mar 1998

L12 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:299919 CAPLUS
DOCUMENT NUMBER: 133:13925
TITLE: Analysis of protein **kinase** specificity using oriented **peptide libraries**
AUTHOR(S): **Songyang, Zhou**; Cantley, Lewis C.
CORPORATE SOURCE: Division of Signal Transduction, Harvard Institutes of Medicine, Beth Israel Hospital, Boston, MA, 02215, USA
SOURCE: Protein Phosphorylation (2nd Edition) (1999), 373-385. Editor(s): Hardie, D. Grahame. Oxford University Press: Oxford, UK.
CODEN: 68XSAT
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 12 refs. This chapter focuses on the use of oriented **peptide libraries** to study the specificities of protein kinases. This approach not only predicts an optimal sequence from a single experiment, with no prior knowledge of in vivo phosphorylation sites required, but it also provides information about the relative importance of each position for selectivity, and about which amino acids are tolerated. The following sections will explain **peptide library** design strategies, detail the exptl. techniques for **peptide** synthesis and selection, and discuss how the data obtained are interpreted.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:800077 CAPLUS
DOCUMENT NUMBER: 130:35386
TITLE: Cyclic **peptide libraries** and methods of use thereof to identify binding motifs
INVENTOR(S): Lai, Hung-sen; Yaffe, Michael B.; **Songyang, Zhou**; Carraway, Kermit L. Iii; Cantley, Lewis C.
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, Inc., USA
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9854577	A1	19981203	WO 1998-US10876	19980528
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 2002068301	A1	20020606	US 1997-864392	19970528
CA 2290993	AA	19981203	CA 1998-2290993	19980528

AU 9876032	A1	19981230	AU 1998-76032	19980528
AU 744707	B2	20020228		
EP 990156	A1	20000405	EP 1998-923835	19980528
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002503231	T2	20020129	JP 1999-500904	19980528
PRIORITY APPLN. INFO.:			US 1997-864392	A 19970528
			WO 1998-US10876	W 19980528

AB Methods for determining an optimal binding motif for a binding compound are provided in which the binding compound is contacted with an oriented degenerate cyclic **peptide library** (ODCPL) under conditions which allow for interaction between the binding compound and the ODCPL such that a complex is formed between the binding compound and a subpopulation of **library** members capable of interacting with the binding compound The subpopulation of **library** members capable of interacting with the binding compound is then separated from **library** members that are incapable of interacting with the binding compound The subpopulation of **library** members capable of interacting with the binding compound is linearized to form a subpopulation of linearized **library** members. The amino acid sequence of the subpopulation of linearized **library** members is determined and an amino acid sequence motif is then determined for an interaction site of the binding compound, based upon the relative abundance of different amino acid residues at each degenerate position within the linearized **library** members. Oriented degenerate cyclic **peptide libraries**, and methods for purifying cyclic peptides from linear peptides, are also provided.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:403481 CAPLUS
DOCUMENT NUMBER: 121:3481
TITLE: Specific motifs recognized by the SH2 domains of Csk, 3BP2, fps/fes, GRB-2, HCP, SHC, Syk, and Vav
AUTHOR(S): **Songyang**, **Z.**; Shoelson, S. E.; McGlade, J.; Olivier, P.; Pawson, T.; Bustelo, X. R.; Barbacid, M.; Sabe, H.; Hanafusa, H.; et al.
CORPORATE SOURCE: Dep. Cell Biol., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Molecular and Cellular Biology (1994), 14(4), 2777-85
CODEN: MCEBD4; ISSN: 0270-7306
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Src homol. 2 (SH2) domains provide specificity to intracellular signaling by binding to specific phosphotyrosine (phospho-Tyr)-containing sequences. The authors recently developed a technique using a degenerate phosphopeptide **library** to predict the specificity of individual SH2 domains src family members, Abl, Nck, Sem5, phospholipase C-γ, p85 subunit of phosphatidylinositol-3-**kinase**, and SHPTP2 (Z. Songyang, S. E. Shoelson, M. Chaudhuri, G. Gish, T. Pawson, W. G. Haser, F. King, T. Roberts, S. Ratnofsky, R. J. Lechleider, B. G. Neel, R. B. Birge, J. E. Fajardo, M. M. Chou, H. Hanafusa, B. Schaffhausen, and L. C. Cantley, Cell, 72:767-778, 1993). The authors report here the optimal recognition motifs for SH2 domains from GRB-2, Drk, Csk, Vav, fps/fes, SHC, Syk (carboxy-terminal SH2), 3BP2, and HCP (amino-terminal SH2 domain, also called PTP1C and SHPTP1). As predicted, SH2 domains from proteins that fall into group I on the basis of a Phe or Tyr at the βD5 position (GRB-2, 3BP2, Csk, fps/fes, Syk C-terminal SH2) select phosphopeptides with the general motif phospho-Tyr-hydrophilic (residue)-hydrophilic (residue)-hydrophobic (residue). The SH2 domains of SHC and HCP (group III proteins with Ile, Leu, or Cys at the βD5

position) selected the general motif phospho-Tyr-hydrophobic-Xxx-hydrophobic, also as predicted. Vav, which has a Thr at the βD5 position, selected phospho-Tyr-Met-Glu-Pro as the optimal motif. Each SH2 domain selected a unique optimal motif distinct from motifs previously determined for other SH2 domains. These motifs are used to predict potential sites in signaling proteins for interaction with specific SH2 domain-containing proteins. The Syk SH2 domain is predicted to bind to Tyr-hydrophilic-hydrophilic-Leu/Ile motifs like those repeated at 10-residue intervals in T- and B-cell receptor-associated proteins. SHC is predicted to bind to a subgroup of these same motifs. A structural basis for the association of Csk with Src family members is also suggested from these studies.

L12 ANSWER 17 OF 18 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004108653 EMBASE
TITLE: An Oriented **Peptide** Array **Library** (OPAL) Strategy to Study Protem-Protein Interactions.
AUTHOR: Rodriguez M.; Li S.S.-C.; Harper J.W.; **Songyang Z.**
CORPORATE SOURCE: M. Rodriguez, Verna/Marrs McLean Dept. of Biochem., Baylor College of Medicine, Houston, TX 77030, United States. songyang@bcm.tmc.edu
SOURCE: Journal of Biological Chemistry, (5 Mar 2004) Vol. 279, No. 10, pp. 8802-8807.
Refs: 37
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040412
Last Updated on STN: 20040412

AB One of the major questions in signal transduction is how the specificities of protein-protein interactions determine the assembly of distinct signaling complexes in response to stimuli. Several **peptide library** methods have been developed and widely used to study protein-protein interactions. These approaches primarily rely on **peptide** or DNA sequencing to identify the **peptide** or consensus motif for binding and may prove too costly or difficult to accommodate high throughput applications. We report here an oriented **peptide** array **library** (OPAL) approach that should facilitate high throughput proteomic analysis of protein-protein interactions. OPAL integrates the principles of both the oriented **peptide libraries** and array technologies. Hundreds of pools of oriented **peptide libraries** are synthesized as amino acid scan arrays. We demonstrate that these arrays can be used to map the specificities of a variety of interactions, including antibodies, protein domains such Src homology 2 domains, and protein kinases.

L12 ANSWER 18 OF 18 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-897562 [82] WPIDS
DOC. NO. NON-CPI: N2003-716358
DOC. NO. CPI: C2003-254839
TITLE: Determining amino acid binding motifs for **kinase** phosphorylation sites is used to find **kinase** inhibitors useful to treat **kinase**-associated disease such as cancer, inflammatory diseases autoimmune disease and transplant rejection.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): CANTLEY, L C; LAI, H; NISHIKAWA, K; **SONGYANG, Z**; YAFFE, M B

PATENT ASSIGNEE(S): (CANT-I) CANTLEY L C; (LAIH-I) LAI H; (NISH-I) NISHIKAWA K; (SONG-I) SONGYANG Z; (YAFF-I) YAFFE M B
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003148377	A1	20030807	(200382)*		43

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003148377	A1 Provisional	US 2000-255586P	20001214
		US 2001-17672	20011214

PRIORITY APPLN. INFO: US 2000-255586P 20001214; US 2001-17672 20011214
AN 2003-897562 [82] WPIDS
AB US2003148377 A UPAB: 20031223
NOVELTY - Determining an amino acid binding motif for a **kinase** phosphorylation site, comprising assessing binding of the **kinase** to a **peptide library** containing a fixed position non-degenerate phosphorylatable amino acid and non-degenerate amino acids and determining bound peptides, is new.

DETAILED DESCRIPTION - Determining an amino acid binding motif for a **kinase** phosphorylation site, comprising:

(a) contacting the **kinase** with a **peptide library**, where each **peptide** has a single non-degenerate phosphorylatable amino acid in a fixed position and degenerate amino acid(s) and allowing the peptides to bind at the **kinase** phosphorylation site;

(b) isolating **kinase-peptide** complexes from the unbound peptides;

(c) releasing the peptides from the **kinase-peptide** complexes and isolating them;

(d) determining the amino acid sequences of the isolated peptides; and

(e) determining an amino acid motif for a binding site of the **kinase** based on the relative abundance of different amino acids at each degenerate position within the peptides.

INDEPENDENT CLAIMS are also included for:

(1) a **kinase** binding molecule comprising a binding motif for a **kinase** phosphorylation site identified by the novel method;

(2) a **kinase** inhibitor comprising a binding motif for a **kinase** phosphorylation site identified using the novel method where the non-degenerate phosphorylatable amino acid is replaced by an amino acid that cannot be phosphorylated by the **kinase** to which it binds;

(3) inhibiting phosphorylation of proteins by a **kinase** comprising contacting the **kinase** with the **kinase** binding molecule or inhibitor;

(4) treating a condition that includes phosphorylation of proteins by a **kinase** comprising administering the **kinase** binding molecule or inhibitor;

(5) validating a **kinase** as a target for inhibition of for the treatment of a condition, comprising:

(a) contacting a molecule comprising a binding motif for a **kinase** phosphorylation site identified by the claimed method with a biological sample containing a **kinase** suspected of being

involved in the condition and allowing binding; and

(b) determining the effect of the molecule on processes mediated by the **kinase**;

(6) inhibiting ZAP-70 **kinase**, comprising contacting ZAP-70 with a claimed **kinase** inhibitor;

(7) treating a condition mediated by ZAP-70 **kinase** comprising administering a claimed **kinase** inhibitor;

(8) inhibiting transcription mediate by a ZAP-70 responsive promoter, comprising contacting a biological sample, cell or organism that comprises a ZAP-70-responsive promoter operably linked to a nucleic acid with a claimed **kinase** inhibitor;

(9) treating a condition mediated by a ZAP-70 **kinase** -mediated promoter, particularly an interleukin (IL)-2 promoter, comprising administering a **kinase** inhibitor;

(10) identifying a **kinase** inhibitor compound, comprising contacting a **kinase**, a **kinase** inhibitor that binds the **kinase** and a candidate **kinase** inhibitor, where either or both inhibitors are labeled, separating bound **kinase** and detecting the amount of candidate inhibitor that has competed with the known inhibitor; and

(11) a **kinase** inhibitor compound identified by the method of (10).

ACTIVITY - Cytostatic; Antiinflammatory; Immunosuppressive.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - The **kinase** inhibitors identified by the method of the invention are used to treat diseases or conditions that result from excessive or unwanted **kinase** activity, including cancer, inflammatory diseases, autoimmune diseases and transplant rejection. The subject may be human or other mammal particularly primate, cow, horse, sheep, pig, goat dog, cat or rodent. (All claimed.) The inhibitors can also be used in diagnosis to detect involvement of a specific **kinase** in a patient or disease model.

Dwg.0/2

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=> e cantley lewis?/au
E1            2     CANTLEY LEWIS L/AU
E2            1     CANTLEY LEWIS S/AU
E3            0 --> CANTLEY LEWIS?/AU
E4           14     CANTLEY LLOYD/AU
E5          104     CANTLEY LLOYD G/AU
E6           26     CANTLEY M/AU
E7            6     CANTLEY M F/AU
E8            6     CANTLEY MARK/AU
E9            1     CANTLEY MARK F/AU
E10           9     CANTLEY P/AU
E11           3     CANTLEY P M/AU
E12           2     CANTLEY R E/AU

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E1            2     CANTLE JOHN/AU
E2            1     CANTLE JOHN EDWARD/AU
E3            0 --> CANTLE L?/AU
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E7            6     CANTLE S J/AU
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E11           1     CANTLER E C/AU
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E2           2     CANTLEY L L/AU
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E8          90     CANTLEY LEWIS/AU
E9         516     CANTLEY LEWIS C/AU
E10         16     CANTLEY LEWIS C JR/AU
E11          2     CANTLEY LEWIS L/AU
E12          1     CANTLEY LEWIS S/AU

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L13        622 "CANTLEY LEWIS"/AU OR "CANTLEY LEWIS C"/AU OR "CANTLEY LEWIS C
               JR"/AU

=> (library or libraries) and l13
L14        114 (LIBRARY OR LIBRARIES) AND L13

=> (peptide or polypeptide) and l14
L15         92 (PEPTIDE OR POLYPEPTIDE) AND L14

=> kinase and l15
L16         43 KINASE AND L15

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17         31 DUP REM L16 (12 DUPLICATES REMOVED)

=> d his

     (FILE 'HOME' ENTERED AT 17:51:21 ON 08 JUL 2005)

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, WPIDS' ENTERED AT 17:51:40 ON 08
     JUL 2005
L1       14659 (LIBRARY OR LIBRARIES) (5A) (PEPTIDE OR POLYPEPTIDE)
L2         394 TYROSINE AND KINASE AND L1
L3         209 PY>2000 AND L2
L4         185 L2 NOT L3
L5          95 DUP REM L4 (90 DUPLICATES REMOVED)
               E SONGYANG ZHOU?/AU
L6     1307952 E1 OR 32
L7         237 E1 OR E2
L8         139 (LIBRARY OR LIBRARIES) AND L7
L9         102 (PEPTIDE OR POLYPEPTIDE) AND L8
L10         66 KINASE AND L9
L11         29 DUP REM L10 (37 DUPLICATES REMOVED)
L12         18 L11 NOT L5
               E CANTLEY LEWIS?/AU
               E CANTLE L?/AU
               E CANTLEY L?/AU
L13        622 E8 OR E9 OR E10
L14        114 (LIBRARY OR LIBRARIES) AND L13
L15         92 (PEPTIDE OR POLYPEPTIDE) AND L14
L16         43 KINASE AND L15
L17         31 DUP REM L16 (12 DUPLICATES REMOVED)

=> l17 not l12
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L18 26 L17 NOT L12

=> l18 not l5
L19 23 L18 NOT L5

=> t ti l19 1-23

L19 ANSWER 1 OF 23 MEDLINE on STN
TI The C2 domain of PKCdelta is a phosphotyrosine binding domain.

L19 ANSWER 2 OF 23 MEDLINE on STN
TI A rapid method for determining protein **kinase** phosphorylation specificity.

L19 ANSWER 3 OF 23 MEDLINE on STN
TI Proteomic screen finds pSer/pThr-binding domain localizing Plk1 to mitotic substrates.

L19 ANSWER 4 OF 23 MEDLINE on STN
TI Hitting the target: emerging technologies in the search for **kinase** substrates.

L19 ANSWER 5 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Scansite 2.0: Proteome-wide prediction of cell signaling interactions using short sequence motifs.

L19 ANSWER 6 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI A motif-based profile scanning approach for genome-wide prediction of signaling pathways.

L19 ANSWER 7 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI **Peptide** and protein **library** screening defines optimal substrate motifs for AKT/PKB.

L19 ANSWER 8 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI A **peptide library** approach identifies a specific inhibitor for the ZAP-70 protein Tyrosine **kinase**.

L19 ANSWER 9 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Utilization of oriented **peptide libraries** to identify substrate motifs selected by ATM.

L19 ANSWER 10 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Analysis of an activator: Coactivator complex reveals an essential role for secondary structure in transcriptional activation.

L19 ANSWER 11 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Sequence specificity of C-terminal Src **kinase** (CSK): A comparison with Src-related kinases c-Fgr and Lyn.

L19 ANSWER 12 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Determination of the specific substrate sequence motifs of protein **kinase** C isozymes.

L19 ANSWER 13 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI A structural basis for substrate specificities of protein Ser/Thr kinases: Primary sequence preference of casein kinases I and II, NIMA, phosphorylase **kinase**, calmodulin-dependent **kinase** II,

CDK5, and Erk1.

L19 ANSWER 14 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Specificity of LIM domain interactions with receptor tyrosine kinases.

L19 ANSWER 15 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Identification of efficient pentapeptide substrates for the tyrosine **kinase** pp60-c-src.

L19 ANSWER 16 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Catalytic specificity of protein-tyrosine kinases is critical for selective signalling.

L19 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
TI Crystal structure of human Polo-like **kinase** Plk1, Polo-box domain-binding phosphopeptide core sequences, and their therapeutic uses for cancer

L19 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
TI The structural basis for substrate and inhibitor selectivity of the anthrax lethal factor

L19 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
TI The affinity-based **peptide library** screening procedure for determination of protein **kinase** binding site motifs and inhibitors, and application to drug design and drug screening

L19 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
TI Inhibitors of phosphoserine- and phosphothreonine-proline-specific isomerases, and therapeutic use

L19 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
TI The use of **peptide library** for the determination of **kinase peptide** substrates

L19 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
TI Recognition and specificity in protein tyrosine **kinase**-mediated signaling

L19 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
TI Use of an oriented **peptide library** to determine the optimal substrates of protein kinases

=> d ibib abs l19 1-23

L19 ANSWER 1 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2005216250 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15851033
TITLE: The C2 domain of PKCdelta is a phosphotyrosine binding domain.
COMMENT: Comment in: Cell. 2005 Apr 22;121(2):158-60. PubMed ID: 15851022
AUTHOR: Benes Cyril H; Wu Ning; Elia Andrew E H; Dharia Tejal; **Cantley Lewis C**; Soltoff Stephen P
CORPORATE SOURCE: Department of Medicine, Division of Signal Transduction, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA.
CONTRACT NUMBER: DE10877 (NIDCR)

DE14721 (NIDCR)
GM56203 (NIGMS)
P30DK34854 (NIDDK)
SOURCE: Cell, (2005 Apr 22) 121 (2) 271-80.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1YRK
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 20050427
Last Updated on STN: 20050601
Entered Medline: 20050531

AB In eukaryotic cells, the SH2 and PTB domains mediate protein-protein interactions by recognizing phosphotyrosine residues on target proteins. Here we make the unexpected finding that the C2 domain of PKCdelta directly binds to phosphotyrosine peptides in a sequence-specific manner. We provide evidence that this domain mediates PKCdelta interaction with a Src binding glycoprotein, CDCP1. The crystal structure of the PKCdelta C2 domain in complex with an optimal phosphopeptide reveals a new mode of phosphotyrosine binding in which the phosphotyrosine moiety forms a ring-stacking interaction with a histidine residue of the C2 domain. This is also the first example of a protein Ser/Thr **kinase** containing a domain that binds phosphotyrosine.

L19 ANSWER 2 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2005149739 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15782149
TITLE: A rapid method for determining protein **kinase** phosphorylation specificity.
COMMENT: Comment in: Nat Methods. 2004 Oct;1(1):13-4. PubMed ID: 15782146
AUTHOR: Hutti Jessica E; Jarrell Emily T; Chang James D; Abbott Derek W; Storz Peter; Toker Alex; **Cantley Lewis C** ; Turk Benjamin E
CORPORATE SOURCE: Division of Signal Transduction, Harvard Medical School, 330 Brookline Avenue, Boston, Massachusetts 02215, USA.
CONTRACT NUMBER: CA75134 (NCI)
GM56203 (NIGMS)
SOURCE: Nat Methods, (2004 Oct) 1 (1) 27-9.
Journal code: 101215604. ISSN: 1548-7091.
PUB. COUNTRY: United States
DOCUMENT TYPE: (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 20050323
Last Updated on STN: 20050525
Entered Medline: 20050524

AB Selection of target substrates by protein kinases is strongly influenced by the amino acid sequence surrounding the phosphoacceptor site. Identification of the preferred **peptide** phosphorylation motif for a given **kinase** permits the production of efficient **peptide** substrates and greatly simplifies the mapping of phosphorylation sites in protein substrates. Here we describe a combinatorial **peptide library** method that allows rapid generation of phosphorylation motifs for serine/threonine kinases.

L19 ANSWER 3 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2003084546 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12595692
TITLE: Proteomic screen finds pSer/pThr-binding domain localizing Plk1 to mitotic substrates.
COMMENT: Comment in: Science. 2003 Feb 21;299(5610):1190-1. PubMed ID: 12595680
AUTHOR: Elia Andrew E H; **Cantley Lewis C**; Yaffe Michael B
CORPORATE SOURCE: Center for Cancer Research, Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.
CONTRACT NUMBER: GM52981 (NIGMS)
GM56203 (NIGMS)
SOURCE: Science, (2003 Feb 21) 299 (5610) 1228-31.
Journal code: 0404511. ISSN: 1095-9203.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030222
Last Updated on STN: 20030331
Entered Medline: 20030328

AB We have developed a proteomic approach for identifying phosphopeptide binding domains that modulate **kinase**-dependent signaling pathways. An immobilized **library** of partially degenerate phosphopeptides biased toward a particular protein **kinase** phosphorylation motif is used to isolate phospho-binding domains that bind to proteins phosphorylated by that **kinase**. Applying this approach to cyclin-dependent kinases (Cdks), we identified the polo-box domain (PBD) of the mitotic **kinase** polo-like **kinase** 1 (Plk1) as a specific phosphoserine (pSer) or phosphothreonine (pThr) binding domain and determined its optimal binding motif. This motif is present in known Plk1 substrates such as Cdc25, and an optimal phosphopeptide containing the motif disrupted PBD-substrate binding and localization of the PBD to centrosomes. This finding reveals how Plk1 can localize to specific sites within cells in response to Cdk phosphorylation at those sites and provides a structural mechanism for targeting the Plk1 **kinase** domain to its substrates.

L19 ANSWER 4 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2002713946 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12475999
TITLE: Hitting the target: emerging technologies in the search for **kinase** substrates.
AUTHOR: Manning Brendan D; **Cantley Lewis C**
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Division of Signal Transduction, Beth Israel Deaconess Medical Center, 4 Blackfan Circle, Boston, MA 02115, USA.
SOURCE: Science's STKE [electronic resource] : signal transduction knowledge environment, (2002 Dec 10) 2002 (162) PE49.
Electronic Publication: 2002-12-10. Ref: 29
Journal code: 100964423. ISSN: 1525-8882.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030105
Entered Medline: 20030103

AB Through phosphorylation, protein kinases can alter the activity,

localization, protein association, and stability of their targets. Despite the importance to our understanding of all aspects of cell biology, progress toward identifying bona fide substrates of specific protein kinases has been slow. Traditionally used techniques to identify true **kinase** substrates, such as genetics, yeast two-hybrid screens, and biochemical purification, are often laborious and unreliable. However, several new approaches have recently been developed and used successfully to identify genuine in vivo substrates of certain protein kinases. These methods include screening for phosphorylation of proteins from phage expression **libraries, peptide library** screens to determine optimal motifs favored by specific kinases, the use of phospho-motif antibodies, and an approach that uses structurally altered kinases and allele-specific adenosine triphosphate analogs and **kinase** inhibitors. We describe these approaches and discuss their utility and inherent caveats.

L19 ANSWER 5 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:438460 BIOSIS
DOCUMENT NUMBER: PREV200300438460
TITLE: Scansite 2.0: Proteome-wide prediction of cell signaling interactions using short sequence motifs.
AUTHOR(S): Obenauer, John C.; **Cantley, Lewis C.**; Yaffe, Michael B. [Reprint Author]
CORPORATE SOURCE: Center for Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Avenue, E18-580, Cambridge, MA, 02139, USA
myaffe@mit.edu
SOURCE: Nucleic Acids Research, (July 1 2003) Vol. 31, No. 13, pp. 3635-3641. print.
ISSN: 0305-1048 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003

AB Scansite identifies short protein sequence motifs that are recognized by modular signaling domains, phosphorylated by protein Ser/Thr- or Tyr-kinases or mediate specific interactions with protein or phospholipid ligands. Each sequence motif is represented as a position-specific scoring matrix (PSSM) based on results from oriented **peptide library** and phage display experiments. Predicted domain-motif interactions from Scansite can be sequentially combined, allowing segments of biological pathways to be constructed in silico. The current release of Scansite, version 2.0, includes 62 motifs characterizing the binding and/or substrate specificities of many families of Ser/Thr- or Tyr-kinases, SH2, SH3, PDZ, 14-3-3 and PTB domains, together with signature motifs for PtdIns(3,4,5)P3-specific PH domains. Scansite 2.0 contains significant improvements to its original interface, including a number of new generalized user features and significantly enhanced performance. Searches of all SWISS-PROT, TrEMBL, Genpept and Ensembl protein database entries are now possible with run times reduced by apprx60% when compared with Scansite version 1.0. Scansite 2.0 allows restricted searching of species-specific proteins, as well as isoelectric point and molecular weight sorting to facilitate comparison of predictions with results from two-dimensional gel electrophoresis experiments. Support for user-defined motifs has been increased, allowing easier input of user-defined matrices and permitting user-defined motifs to be combined with pre-compiled Scansite motifs for dual motif searching. In addition, a new series of Sequence Match programs for non-quantitative user-defined motifs has been implemented. Scansite is available via the World Wide Web at http://scansite.mit.edu.

L19 ANSWER 6 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:226171 BIOSIS
DOCUMENT NUMBER: PREV200100226171
TITLE: A motif-based profile scanning approach for genome-wide prediction of signaling pathways.
AUTHOR(S): Yaffe, Michael B. [Reprint author]; Leparc, German G.; Lai, Jack; Obata, Toshiyuki; Volinia, Stefano; **Cantley, Lewis C.**
CORPORATE SOURCE: Division of Signal Transduction, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Institutes of Medicine, 330 Brookline Ave., 10th Floor, Boston, MA, 02215, USA
myaffe@mit.edu
SOURCE: Nature Biotechnology, (April, 2001) Vol. 19, No. 4, pp. 348-353. print.
ISSN: 1087-0156.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 May 2001
Last Updated on STN: 18 Feb 2002

AB The rapid increase in genomic information requires new techniques to infer protein function and predict protein-protein interactions. Bioinformatics identifies modular signaling domains within protein sequences with a high degree of accuracy. In contrast, little success has been achieved in predicting short linear sequence motifs within proteins targeted by these domains to form complex signaling networks. Here we describe a **peptide library**-based searching algorithm, accessible over the World Wide Web, that identifies sequence motifs likely to bind to specific protein domains such as 14-3-3, SH2, and SH3 domains, or likely to be phosphorylated by specific protein kinases such as Src and AKT. Predictions from database searches for proteins containing motifs matching two different domains in a common signaling pathway provides a much higher success rate. This technology facilitates prediction of cell signaling networks within proteomes, and could aid in the identification of drug targets for the treatment of human diseases.

L19 ANSWER 7 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:12666 BIOSIS
DOCUMENT NUMBER: PREV200100012666
TITLE: **Peptide** and protein **library** screening defines optimal substrate motifs for AKT/PKB.
AUTHOR(S): Obata, Toshiyuki; Yaffe, Michael B.; Leparc, German G.; Piro, Elizabeth T.; Maegawa, Hiroshi; Kashiwagi, Atsunori; Kikkawa, Ryuichi; **Cantley, Lewis C.** [Reprint author]
CORPORATE SOURCE: Division of Signal Transduction, Harvard Institutes of Medicine, 330 Brookline Ave., 10th Floor, Boston, MA, 02215, USA
cantley@helix.mgh.harvard.edu
SOURCE: Journal of Biological Chemistry, (Novemeber, 2000) Vol. 275, No. 46, pp. 36108-36115. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Dec 2000
Last Updated on STN: 15 Feb 2002

AB AKT was originally identified as a proto-oncogene with a pleckstrin homology and Ser/Thr protein **kinase** domains. Recent studies revealed that AKT regulates a variety of cellular functions including cell survival, cell growth, cell differentiation, cell cycle progression, transcription, translation, and cellular metabolism. To clarify the substrate specificity of AKT, we have used an oriented **peptide library** approach to determine optimal amino acids at positions

N-terminal and C-terminal to the site of phosphorylation. The predicted optimal **peptide** substrate (Arg-Lys-Arg-Xaa-Arg-Thr-Tyr-Ser*-Phe-Gly where Ser* is the phosphorylation site) has similarities to but is distinct from optimal substrates that we previously defined for related basophilic protein kinases such as protein **kinase** A, Ser/Arg-rich kinases, and protein **kinase** C family members. The positions most important for high Vmax/Km ratio were Arg-3>Arg-5>Arg-7. The substrate specificity of AKT was further investigated by screening a lambdaGEX phage HeLa cell cDNA expression **library**. All of the substrates identified by this procedure contained Arg-Xaa-Arg-Xaa-Xaa-(Ser/Thr) motifs and were in close agreement with the motif identified by **peptide library** screening. The results of this study should help in prediction of likely AKT substrates from primary sequences.

L19 ANSWER 8 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:1144 BIOSIS
DOCUMENT NUMBER: PREV200100001144
TITLE: A **peptide library** approach identifies a specific inhibitor for the ZAP-70 protein Tyrosine **kinase**.
AUTHOR(S): Nishikawa, Kiyotaka; Sawasdikosol, Sansana; Fruman, David A.; Lai, Jack; Songyang, Zhou; Burakoff, Steven J.; Yaffe, Michael B.; **Cantley, Lewis C.** [Reprint author]
CORPORATE SOURCE: Division of Signal Transduction, Department of Cell Biology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02115, USA cantley@helix.mgh.harvard.edu
SOURCE: Molecular Cell, (October, 2000) Vol. 6, No. 4, pp. 969-974. print.
ISSN: 1097-2765.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Dec 2000
Last Updated on STN: 21 Dec 2000

AB We utilized a novel **peptide library** approach to identify specific inhibitors of ZAP-70, a protein Tyr **kinase** involved in T cell activation. By screening more than 6 billion peptides oriented by a common Tyr residue for their ability to bind to ZAP-70, we determined a consensus optimal **peptide**. A Phe-for-Tyr substituted version of the **peptide** inhibited ZAP-70 protein Tyr **kinase** activity by competing with protein substrates (KI of 2 muM). The related protein Tyr kinases, Lck and Syk, were not significantly inhibited by the **peptide**. When introduced into intact T cells, the **peptide** blocked signaling downstream of ZAP-70, including ZAP-70-dependent gene induction, without affecting upstream Tyr phosphorylation. Thus, screening Tyr-oriented **peptide libraries** can identify selective **peptide** inhibitors of protein Tyr kinases.

L19 ANSWER 9 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:398059 BIOSIS
DOCUMENT NUMBER: PREV200000398059
TITLE: Utilization of oriented **peptide libraries** to identify substrate motifs selected by ATM.
AUTHOR(S): O'Neill, Ted; Dwyer, Alison J.; Ziv, Yael; Chan, Doug W.; Lees-Miller, Susan P.; Abraham, Robert H.; Lai, Jack H.; Hill, David; Shiloh, Yossi; **Cantley, Lewis C.**; Rathbun, Gary A. [Reprint author]
CORPORATE SOURCE: Center for Blood Research, Dept. of Pediatrics, Children's Hospital, Harvard Medical School, 200 Longwood Ave., Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry, (July 28, 2000) Vol. 275,

No. 30, pp. 22719-22727. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Sep 2000
Last Updated on STN: 8 Jan 2002

AB The ataxia telangiectasia mutated (ATM) gene encodes a serine/threonine protein **kinase** that plays a critical role in genomic surveillance and development. Here, we use a **peptide library** approach to define the in vitro substrate specificity of ATM **kinase** activity. The **peptide library** analysis identified an optimal sequence with a central core motif of LSQE that is preferentially phosphorylated by ATM. The contributions of the amino acids surrounding serine in the LSQE motif were assessed by utilizing specific **peptide libraries** or individual **peptide** substrates. All amino acids comprising the LSQE sequence were critical for maximum **peptide** substrate suitability for ATM. The DNA-dependent protein **kinase** (DNA-PK), a Ser/Thr **kinase** related to ATM and important in DNA repair, was compared with ATM in terms of **peptide** substrate selectivity. DNA-PK was found to be unique in its preference of neighboring amino acids to the phosphorylated serine. **Peptide library** analyses defined a preferred amino acid motif for ATM that permits clear distinctions between ATM and DNA-PK **kinase** activity. Data base searches using the **library**-derived ATM sequence identified previously characterized substrates of ATM, as well as novel candidate substrate targets that may function downstream in ATM-directed signaling pathways.

L19 ANSWER 10 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:472650 BIOSIS
DOCUMENT NUMBER: PREV199800472650
TITLE: Analysis of an activator: Coactivator complex reveals an essential role for secondary structure in transcriptional activation.
AUTHOR(S): Parker, David; Jhala, Ulupi S.; Radhakrishnan, Ishwar; Yaffe, Michael B.; Reyes, Christine; Shulman, Andrew I.; **Cantley, Lewis C.**; Wright, Peter E.; Montminy, Marc [Reprint author]
CORPORATE SOURCE: Joslin Diabetes Center Research Division, Boston, MA 02215, USA
SOURCE: Molecular Cell, (Sept., 1998) Vol. 2, No. 3, pp. 353-359. print.
ISSN: 1097-2765.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 1998
Last Updated on STN: 5 Nov 1998

AB Ser-133 phosphorylation of CREB within the **kinase**-inducible domain (KID) promotes target gene activation via complex formation with the KIX domain of the coactivator CBP. Concurrent phosphorylation of CREB at Ser-142 inhibits transcriptional induction via an unknown mechanism. Unstructured in the free state, KID folds into a helical structure upon binding to KIX. Using site-directed mutagenesis based on the NMR structure of the KID:KIX complex, we have examined the mechanisms by which Ser-133 and Ser-142 phosphorylation regulate CRED activity. Our results indicate that phosphate-Ser-133 stabilizes whereas phospho-Ser-142 disrupts secondary structure-mediated interactions between CREB may CBP. Thus, differential phosphorylation of CREB may form the basis by which upstream signals regulate the specificity of target gene activation.

L19 ANSWER 11 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:318771 BIOSIS
DOCUMENT NUMBER: PREV199799609259
TITLE: Sequence specificity of C-terminal Src **kinase** (CSK): A comparison with Src-related kinases c-Fgr and Lyn.
AUTHOR(S): Ruzzene, Maria; Songyang, Zhou; Marin, Oriano; Donella-Deana, Arianna; Brunati, Anna Maria; Guerra, Barbara; Agostinis, Patrizia; **Cantley, Lewis C.**; Pinna, Lorenzo A. [Reprint author]
CORPORATE SOURCE: Dipartimento Chimica Biol., Univ. Padova, Viale G. Colombo 3, I-35121 Padova, Italy
SOURCE: European Journal of Biochemistry, (1997) Vol. 246, No. 2, pp. 433-439.
CODEN: EJBCAI. ISSN: 0014-2956.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jul 1997
Last Updated on STN: 4 Sep 1997

AB An eicosapeptide encompassing the C-terminal tail of c-Src (Tyr527) which is conserved in most Srcrelated protein kinases, is phosphorylated by C-terminal Src **kinase** (CSK) and by the two Src-related protein kinases c-Fgr and Lyn, with similar kinetic constants. Two related peptides reproducing the C-terminal segments of c-Src mutants defective in CSK phosphorylation (MacAuley, A., Okada, M., Nada, S., Nakagawa, H. fwdarw Cooper, J. A. (1993) Oncogene 8, 117-124) AFLEDSCTGTEPLYQRGENL (mutant number 28) and AFLEDFTGTKPQYHPGENL (mutant number 29), proved a better and a much worse substrates, respectively than the wild-type **peptide**, with either CSK or the two Src kinases. By changing individual residues in the best **peptide** substrate, it was shown that the main element responsible for its improved phosphorylation is leucine at position -1 (instead of glutamine), while lysine at position -3 (instead of glutamate) has a detrimental effect, possibly accounting for the negligible phosphorylation of **peptide** derived from mutant number 29. By contrast to most **peptide** substrates, including the Src C-terminal peptides, which exhibit relatively high K-m values, a polyoma-virus-middle-T-antigen-(mT)-derived **peptide** with tyrosine embedded in a highly hydrophobic sequence (EEEPQFEEIPIYLELLP) exhibits with CSK a quite low K-m value (63 mu-M). Consistent with this, the optimal sequence selected by CSK in an oriented **peptide library** is XXXIYMFFF. This is different from sequences selected by Lyn (DEEIYEELX) and c-Fgr (XEEIYGIFF), although they all share a high selection for a hydrophobic residue at n-1. In sharp contrast, TPKIIB/p38-srk, related to the catalytic domain of p72-syk selects acidic residues at nearly all positions, n-1 included. These data support the notion that the features determining the specific phosphorylation of the C-terminal tyrosine residue of Src do not reside in the primary structure surrounding the target tyrosine. They also show that this site does not entirely fulfil the optimal consensus sequence recognized by CSK, disclosing the possibility that as yet unrecognized CSK targets structurally unrelated to the C-terminal tyrosine residue of Src kinases may exist.

L19 ANSWER 12 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:63991 BIOSIS
DOCUMENT NUMBER: PREV199799363194
TITLE: Determination of the specific substrate sequence motifs of protein **kinase** C isozymes.
AUTHOR(S): Nishikawa, Kiyotaka [Reprint author]; Toker, Alex; Johannes, Franz-Josef; Songyang, Zhou; **Cantley, Lewis C.**

CORPORATE SOURCE: Beth Israel Hosp., Div. Signal Transduction, Harvard Inst. Med., 10th Floor, 330 Brookline Ave., Boston, MA 02215, USA
SOURCE: Journal of Biological Chemistry, (1997) Vol. 272, No. 2, pp. 952-960.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Feb 1997
Last Updated on STN: 11 Feb 1997

AB Protein **kinase** C (PKC) family members play significant roles in a variety of intracellular signal transduction processes, but information about the substrate specificities of each PKC family member is quite limited. In this study, we have determined the optimal **peptide** substrate sequence for each of nine human PKC isozymes (alpha, beta-I, beta-II, gamma, delta, epsilon, eta, mu, and zeta) by using an oriented **peptide library**. AR PKC isozymes preferentially phosphorylated peptides with hydrophobic amino acids at position +1 carboxyl-terminal of the phosphorylated Ser and basic residues at position -3. All isozymes, except PKC-mu, selected peptides with basic amino acids at positions -6, -4, and -2. PKC-alpha, -beta-I, -beta-II, -gamma, and -eta selected peptides with basic amino acid at positions +2, +3, and +4, but PKC-delta, -epsilon, -zeta, and -mu preferred peptides with hydrophobic amino acid at these positions. At position -5, the selectivity was quite different among the various isozymes; PKC-alpha, -gamma, and -delta selected peptides with Arg at this position while other PKC isozymes selected hydrophobic amino acids such as Phe, Leu, or Val. Interestingly, PKC-mu showed extreme selectivity for peptides with Leu at this position. The predicted optimal sequences from position -3 to +2 for PKC-alpha, -beta-I, -beta-II, -gamma, -delta, and -eta were very similar to the endogenous pseudosubstrate sequences of these PKC isozymes, indicating that these core regions may be important to the binding of corresponding substrate peptides. Synthetic peptides based on the predicted optimal sequences for PKC-alpha, -beta-I, -delta, -zeta, and -mu were prepared and used for the determination of K-m and V-max for these isozymes. As judged by V-max/K-m values, these peptides were in general better substrates of the corresponding isozymes than those of the other PKC isozymes, supporting the idea that individual PKC isozymes have distinct optimal substrates. The structural basis for the selectivity of PKC isozymes is discussed based on residues predicted to form the catalytic cleft.

L19 ANSWER 13 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1996:536634 BIOSIS
DOCUMENT NUMBER: PREV199699258990
TITLE: A structural basis for substrate specificities of protein Ser/Thr kinases: Primary sequence preference of casein kinases I and II, NIMA, phosphorylase **kinase**, calmodulin-dependent **kinase** II, CDK5, and Erk1.
AUTHOR(S): Songyang, Z.; Lu, Kun Ping; Kwon, Young T.; Tsai, Li-Huei; Filhol, Odile; Cochet, Claude; Brickey, Debra A.; Soderling, Thomas R.; Bartleson, Cheryl; Graves, Donald J.; Demaggio, Anthony J.; Hoekstra, Merl F.; Blenis, John; Hunter, Tony; **Cantley, Lewis C.** [Reprint author]
CORPORATE SOURCE: Div. Signal Transduction, Beth Israel Hosp., 330 Brookline Ave., Boston, MA 02115, USA
SOURCE: Molecular and Cellular Biology, (1996) Vol. 16, No. 11, pp. 6486-6493.
CODEN: MCEBD4. ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1996

Last Updated on STN: 23 Jan 1997

AB We have developed a method to study the primary sequence specificities of protein kinases by using an oriented degenerate **peptide library**. We report here the substrate specificities of eight protein Ser/Thr kinases. All of the kinases studied selected distinct optimal substrates. The identified substrate specificities of these kinases, together with known crystal structures of protein **kinase** A, CDK2, Erk2, twitchin, and casein **kinase** I, provide a structural basis for the substrate recognition of protein Ser/Thr kinases. In particular, the specific selection of amino acids at the +1 and -3 positions to the substrate serine/threonine can be rationalized on the basis of sequences of protein kinases. The identification of optimal **peptide** substrates of CDK5, casein kinases I and II, NIMA, calmodulin-dependent kinases, Erk1, and phosphorylase **kinase** makes it possible to predict the potential in vivo targets of these kinases.

L19 ANSWER 14 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1996:363307 BIOSIS
DOCUMENT NUMBER: PREV199699085663
TITLE: Specificity of LIM domain interactions with receptor tyrosine kinases.
AUTHOR(S): Wu, Rui-Yun; Durick, Kyle; Songyang, Zhou; **Cantley, Lewis C.**; Taylor, Susan S.; Gill, Gordon N. [Reprint author]
CORPORATE SOURCE: Univ. California San Diego, 9500 Gilman Dr., 0650, La Jolla, CA 92093-0650, USA
SOURCE: Journal of Biological Chemistry, (1996) Vol. 271, No. 27, pp. 15934-15941.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Aug 1996
Last Updated on STN: 15 Aug 1996

AB LIM domains, Cys-rich motifs containing approximately 50 amino acids found in a variety of proteins, are proposed to direct protein-protein interactions. To identify structural targets recognized by LIM domains, we have utilized random **peptide library** selection, the yeast two-hybrid system, and glutathione S-transferase fusions. Enigma contains three LIM domains within its carboxyl terminus and LIM3 of Enigma specifically recognizes active but not mutant endocytic codes of the insulin receptor (InsR) (Wu, R. Y., and Gill, G. N. (1994) J. Biol. Chemical 269, 25085-25090). Interaction of two random **peptide libraries** with glutathione S-transferase-LIM3 of Enigma indicated specific binding to Gly-Pro-Hyd-Gly-Pro-Hyd-Tyr-Ala corresponding to the major endocytic code of InsR. **Peptide** competition demonstrated that both Pro and Tyr residues were required for specific interaction of InsR with Enigma. In contrast to LIM3 of Enigma binding to InsR, LIM2 of Enigma associated specifically with the receptor tyrosine **kinase**, Ret. Ret was specific for LIM2 of Enigma and did not bind other LIM domains tested. Mutational analysis indicated that the residues responsible for binding to Enigma were localized to the carboxyl-terminal 61 amino acids of Ret. A **peptide** corresponding to the carboxyl-terminal 20 amino acids of Ret dissociated Enigma and Ret complexes, while a mutant that changed Asn-Lys-Leu-Tyr in the **peptide** to Ala-Lys-Leu-Ala or a **peptide** corresponding to exon16 of InsR failed to disrupt the complexes, indicating the Asn-Lys-Leu-Tyr sequence of Ret is essential to the recognition motif for LIM2 of Enigma. We conclude that LIM domains of Enigma recognize tyrosine-containing motifs with specificity residing in both the LIM domains and in the target structures.

L19 ANSWER 15 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1995:551640 BIOSIS
DOCUMENT NUMBER: PREV199698565940
TITLE: Identification of efficient pentapeptide substrates for the tyrosine **kinase** pp60-c-src.
AUTHOR(S): Nair, Shrikumar A.; Kim, Moon H.; Warren, Stephen D.; Choi, Sun; Songyang, Zhou; **Cantley, Lewis C.**; Hangauer, David G. [Reprint author]
CORPORATE SOURCE: Dep. Med. Chem., State Univ. N.Y. Buffalo, Buffalo, NY 14260-1200, USA
SOURCE: Journal of Medicinal Chemistry, (1995) Vol. 38, No. 21, pp. 4276-4283.
CODEN: JMCMAR. ISSN: 0022-2623.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Dec 1995
Last Updated on STN: 31 Dec 1995

AB The development of inhibitors of protein tyrosine kinases (PTKs) is a promising approach to obtaining new therapeutic agents for a variety of diseases, particularly cancer. However, the discovery of **peptide** -based inhibitors has been hindered by the lack of small **peptide** substrate sequences (i.e. five residues or less) with which a variety of inhibitor designs could be readily evaluated by replacing the Tyr with natural and unnatural amino acids. These prototypical small **peptide** inhibitors could then form the basis for designing analogous conformationally constrained, **peptide**-mimetic or non-**peptide** inhibitors with improved therapeutic potential. In this study we have identified the best known small **peptide** substrate for the PTK pp60-c-src, which is the parent of the src family of nonreceptor PTKs. This pentapeptide substrate, Ac-Ile-Tyr-Gly-Glu-Phe-NH-2, has a K-m of 368 mu-M and V-max of 1.02 mu-mol/min/mg when tested utilizing the assay methodology of Budde et al. (Anal. Biochem. 1992, 200, 347-351) after a series of modifications were made to more closely simulate the conditions inside a typical mammalian cell. This substrate was designed from information obtained by Songyang et al. (Nature 1995, 373, 536-539) with a 2.5 billion member combinatorial **library** of **peptide** substrates for pp60-c-src. A second pentapeptide substrate, Ac-Glu-Asp-Ala-Ile-Tyr-NH-2, with a weaker binding affinity (K-m = 880 mu-M) but improved V-max (1.86 mu-mol/min/mg), was also identified. This **peptide** was designed from the pp60-c-src autophosphorylation sequence and information obtained by Songyang et al. (Ibid.) and Till et al. (J. Biol. Chemical 1994, 269, 7423-7428) with combinatorial **libraries** of **peptide** substrates. These new substrates provide sufficient binding affinities and rates of phosphorylation to be utilized for evaluating the relative effectiveness of various reversible and mechanism-based irreversible inhibitor designs for pp60-c-src while appended to easily prepared small peptides.

L19 ANSWER 16 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1995:170670 BIOSIS
DOCUMENT NUMBER: PREV199598184970
TITLE: Catalytic specificity of protein-tyrosine kinases is critical for selective signalling.
AUTHOR(S): Zhou, Songyang; Carrawayi, Kermit L. Ii; Eck, Michael J.; Harrison, Stephen C.; Feldman, Ricardo A.; Mohammadi, Moosa; Schlessinger, Joseph; Hubbard, Stevan R.; Smith, Darrin P.; Eng, Charis; Lorenzo, Marla J.; Ponder, Bruce A. J.; Mayer, Bruce J.; **Cantley, Lewis C.** [Reprint author]

CORPORATE SOURCE: Dep. Cell Biol., Harvard Med. Sch., Boston, MA 02215, USA
SOURCE: Nature (London), (1995) Vol. 373, No. 6514, pp. 536-539.
CODEN: NATUAS. ISSN: 0028-0836.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Apr 1995
Last Updated on STN: 27 Apr 1995

AB How do distinct protein-tyrosine kinases activate specific downstream events? Src-homology-2 (SH2) domains on tyrosine kinases or targets of tyrosine kinases recognize phosphotyrosine in a specific sequence context and thereby provide some specificity. The role of the catalytic site of tyrosine kinases in determining target specificity has not been fully investigated. Here we use a degenerate **peptide library** to show that each of nine tyrosine kinases investigated has a unique optimal **peptide** substrate. We find that the cytosolic tyrosine kinases preferentially phosphorylate peptides recognized by their own SH2 domains or closely related SH2 domains (group I; reference 3), whereas receptor tyrosine kinases preferentially phosphorylate peptides recognized by subsets of group III SH2 domains. The importance of these findings for human disease is underscored by our observation that a point mutation in the RET receptor-type tyrosine **kinase**, which causes multiple endocrine neoplasia type 2B, results in a shift in **peptide** substrate specificity.

L19 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:453338 CAPLUS
DOCUMENT NUMBER: 141:19612
TITLE: Crystal structure of human Polo-like **kinase** Plk1, Polo-box domain-binding phosphopeptide core sequences, and their therapeutic uses for cancer
INVENTOR(S): Yaffe, Michael B.; Elia, Andrew E. H.; Rellos, Peter; **Cantley, Lewis C.**; Smerdon, Stephen J.; Mancke, Isaac
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 317 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004046317	A2	20040603	WO 2003-US36392	20031114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2002-426132P P 20021114
US 2003-485641P P 20030708
US 2003-487899P P 20030717

OTHER SOURCE(S): MARPAT 141:19612

AB The present invention relates to therapeutic compds. and methods of use of these therapeutic compds. for treating cellular proliferative disorders. The invention also provides three-dimensional structures of a Polo-like **kinase** and methods for designing or selecting small mol.

inhibitors using these structures, and the therapeutic use of such compds. The invention also includes a method for identifying phosphopeptide-binding domains by screening **peptide libraries**. The carboxy-terminal region of the cell cycle regulating **kinase** Plk-1 encodes a phosphopeptide recognition domain that consists of the non-**kinase** region of the protein (amino acids 326-603), called the Polo-box domain. The crystal structure of human Plk-1 Polo-box domain in complex with its optimal phosphothreonine-containing **peptide** was determined to identify the structural basis for Polo-box domain activity. Site-directed mutagenesis showed that phosphoserine/threonine-dependent binding is a general feature of Polo-box domain activity in the Plk family and is important for the function of the domain in **kinase** targeting to substrates and in in vitro activity of the **kinase** domain. A **library** of partially degenerate phosphopeptides was also used to identify phosphopeptide-binding modules mediating signaling in the DNA damage response pathway. Tandem BRCT domains in the proteins PTIP and BRCA1 were identified as phosphoserine- or phosphothreonine-specific binding modules that recognize a subset of ATM and ATR substrates following γ-irradiation

L19 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:106977 CAPLUS
DOCUMENT NUMBER: 140:316981
TITLE: The structural basis for substrate and inhibitor selectivity of the anthrax lethal factor
AUTHOR(S): Turk, Benjamin E.; Wong, Thiang Yian; Schwarzenbacher, Robert; Jarrell, Emily T.; Leppla, Stephen H.; Collier, R. John; Liddington, Robert C.; **Cantley, Lewis C.**
CORPORATE SOURCE: Department of Cell Biology, Beth Israel Deaconess Medical Center, Department of Medicine, Division of Signal Transduction, Harvard Medical School, Boston, MA, 02215, USA
SOURCE: Nature Structural & Molecular Biology (2004), 11(1), 60-66
CODEN: NSMBCU; ISSN: 1545-9993
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent events have created an urgent need for new therapeutic strategies to treat anthrax. We have applied a mixture-based **peptide library** approach to rapidly determine the optimal **peptide** substrate for the anthrax lethal factor (LF), a metalloproteinase with an important role in the pathogenesis of the disease. Using this approach we have identified **peptide** analogs that inhibit the enzyme in vitro and that protect cultured macrophages from LF-mediated cytolysis. The crystal structures of LF bound to an optimized **peptide** substrate and to **peptide**-based inhibitors provide a rationale for the observed selectivity and may be exploited in the design of future generations of LF inhibitors.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:609969 CAPLUS
DOCUMENT NUMBER: 139:175859
TITLE: The affinity-based **peptide library** screening procedure for determination of protein **kinase** binding site motifs and inhibitors, and application to drug design and drug screening
INVENTOR(S): Nishikawa, Kiyotaka; Lai, Hung-sen; Zhou, Songyang; Yaffe, Michael B.; **Cantley, Lewis C.**

PATENT ASSIGNEE(S): Japan
SOURCE: U.S. Pat. Appl. Publ., 43 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003148377	A1	20030807	US 2001-17672		20011214
PRIORITY APPLN. INFO.:			US 2000-255586P	P	20001214

AB The invention provides methods for rapidly determining **kinase** binding site motifs using a oriented degenerate **peptide library** approach. The methods involve the selection of peptides by binding affinity. Inhibitors of protein kinases that include or compete for the binding site motifs determined using the methods also are provided, as are methods and compns. for using these binding site motifs and inhibitors. The affinity-based **peptide library** screening procedure to determine a high-affinity and high-specificity ZAP-70 **kinase** inhibitor is disclosed. The method presented here is widely applicable for the design of highly selective inhibitors for other protein kinases.

L19 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:194172 CAPLUS
DOCUMENT NUMBER: 130:232474
TITLE: Inhibitors of phosphoserine- and phosphothreonine-proline-specific isomerases, and therapeutic use
INVENTOR(S): Lu, Kun Ping; **Cantley, Lewis C.**; Yaffee, Michael; Fischer, Gunter
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA; Max-Planck-Gesellschaft zur Forderung der Wissenschaften E.V.
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9912962	A1	19990318	WO 1998-US18862		19980904
W: CA, JP					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
US 6462173	B1	20021008	US 1997-988842		19971211
CA 2303462	AA	19990318	CA 1998-2303462		19980904
AU 9927032	A1	19990524	AU 1999-27032		19980904
AU 751271	B2	20020808			
EP 1012178	A1	20000628	EP 1998-946921		19980904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001515917	T2	20010925	JP 2000-510767		19980904
US 2003109423	A1	20030612	US 2002-193768		20020710
PRIORITY APPLN. INFO.:			US 1997-58164P	P	19970908
			US 1997-988842	A	19971211
			WO 1998-US18862	W	19980904

AB Peptides and **peptide** mimetics that inhibit phosphoserine- or phosphothreonine-specific peptidyl prolyl isomerases are described. The inhibitor compds. of the invention are useful in the treatment of disorders of cell proliferation, e.g. hyperplastic or neoplastic

disorders, wherein treatment of the disorder with the inhibitor results in the arrest of mitosis and apoptosis of the target cells.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:376353 CAPLUS
DOCUMENT NUMBER: 129:158213
TITLE: The use of **peptide library** for the determination of **kinase peptide** substrates
AUTHOR(S): Zhou, Songyang; **Cantley, Lewis C.**
CORPORATE SOURCE: Harvard Medical School, Beth Israel Hospital, Boston, MA, USA
SOURCE: Methods in Molecular Biology (Totowa, New Jersey) (1998), 87(Combinatorial Peptide Library Protocols), 87-98
CODEN: MMBIED; ISSN: 1064-3745
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 11 refs.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:959586 CAPLUS
DOCUMENT NUMBER: 124:3543
TITLE: Recognition and specificity in protein tyrosine **kinase**-mediated signaling
AUTHOR(S): Songyang, Zhou; **Cantley, Lewis C.**
CORPORATE SOURCE: Beth Israel Hosp., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Trends in Biochemical Sciences (1995), 20(11), 470-5
CODEN: TBSCDB; ISSN: 0376-5067
PUBLISHER: Elsevier Trends Journals
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 46 refs. There are several factors that contribute to the specificities of protein tyrosine kinases (PTKs) in signal transduction pathways. While protein-protein interaction domains, such as the Src homol. (SH2 and SH3) domains, regulate the cellular localization of PTKs and their substrates, the specificities of PTKs are ultimately determined by their catalytic domains. The use of **peptide libraries** has revealed the substrate specificities of SH2 domains and PTK catalytic domains, and has suggested cross-talk between these domains.

L19 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:206803 CAPLUS
DOCUMENT NUMBER: 122:285133
TITLE: Use of an oriented **peptide library** to determine the optimal substrates of protein kinases
AUTHOR(S): Songyang, Zhou; Blechner, Steven; Hoagland, Nicole; Hoekstra, Merl F.; Piwnica-Worms, Helen; **Cantley, Lewis C.**
CORPORATE SOURCE: Div. Signal Transduction, Beth Israel Hosp., Boston, MA, 02215, USA
SOURCE: Current Biology (1994), 4(11), 973-82
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Current Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have developed a new technique for determining the substrate specificity of protein kinases, using an oriented **library** of >2.5 billion **peptide** substrates. In this approach, the consensus sequence of optimal substrates is determined by sequencing the mixture of products generated during a brief reaction with the **kinase** of interest. The optimal substrate predicted for cAMP-dependent protein **kinase** (PKA) by this technique is consistent with the sequences of known PKA substrates. The optimal sequences predicted for cyclin-dependent kinases (CKDs) cyclin B-Cdc2 and cyclin A-CDK2 also agree well with sites thought to be phosphorylated in vivo by these kinases. In addition, the optimal substrate was determined for SLK1, a homolog of the STE20 protein serine **kinase** of hitherto unknown substrate specificity. A model incorporating the optimal cyclin B-Cdc2 substrate into the known crystal structure of this **kinase** was also discussed. Using the new technique, the sequence specificity of protein kinases can rapidly be predicted and, from this information, potential targets of the kinases can be identified.

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(FILE 'HOME' ENTERED AT 17:51:21 ON 08 JUL 2005)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, WPIDS' ENTERED AT 17:51:40 ON 08 JUL 2005

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L1         14659 (LIBRARY OR LIBRARIES) (5A) (PEPTIDE OR POLYPEPTIDE)
L2           394 TYROSINE AND KINASE AND L1
L3           209 PY>2000 AND L2
L4           185 L2 NOT L3
L5            95 DUP REM L4 (90 DUPLICATES REMOVED)
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L7           237 E1 OR E2
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L10           66 KINASE AND L9
L11           29 DUP REM L10 (37 DUPLICATES REMOVED)
L12           18 L11 NOT L5
                 E CANTLEY LEWIS?/AU
                 E CANTLE L?/AU
                 E CANTLEY L?/AU
L13          622 E8 OR E9 OR E10
L14          114 (LIBRARY OR LIBRARIES) AND L13
L15           92 (PEPTIDE OR POLYPEPTIDE) AND L14
L16           43 KINASE AND L15
L17           31 DUP REM L16 (12 DUPLICATES REMOVED)
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L19           23 L18 NOT L5
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